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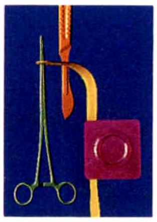

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References: **1.** Nightingale CH, Smith KS, Quintiliani R, et al: The conversion of cefoxitin usage to cefotetan: An interdisciplinary approach. *Am J Surg* 1988;155(5A):101-102. **2.** Sochalski A, Sullman S, Andriole VT: Cost-effectiveness study of cefotetan versus cefoxitin and cefotetan versus combination antibiotic regimens. *Am J Surg* 1988;155(5A):96-101. **3.** CEFOTAN® (cefotetan disodium) full prescribing information issued March 1986. **4.** *Physicians' Desk Reference*, ed 43. Oradell, NJ, Medical Economics Co, 1989. Mefoxin® (cefoxitin sodium, MSD), pp 1355-1357. **5.** Carver M, Quintiliani R, Nightingale CH: Comparative pharmacokinetic study of cefotetan and cefoxitin in healthy volunteers. *Infect Surg*, April 1986 (suppl), pp 11-14. **6.** Quintiliani R, Nightingale CH, Stevens RC, et al: Comparative pharmacokinetics of cefotetan and cefoxitin in patients undergoing hysterectomies and colorectal operations. *Am J Surg* 1988;155(5A):67-70.

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A Monthly Review of Surgical Science and Practice

Annals of Surgery

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The Fetus as a Patient 277

James A. O'Neill, Jr., M.D.
Philadelphia, Pennsylvania

WHAT'S NEW IN GENERAL SURGERY

The Fetus as a Patient: Surgical Considerations 279

The diagnosis and treatment of human fetal defects has evolved rapidly in the past decade due to improved fetal imaging techniques and better understanding of fetal pathophysiology derived from animal models. The detection of a fetal anomaly now may lead to a change in the timing of delivery, in the mode of delivery, or in prenatal treatment. Because most therapeutic maneuvers involve some risk to the fetus and mother, there must be a reasonable expectation that the procedure is feasible, safe, and effective before it can be attempted in humans. This requires reliable information about the pathophysiology and natural history of the disease process, the efficacy of fetal surgical intervention in ameliorating the disease, and the feasibility and safety of the proposed intervention. This article focuses on the rationale and initial clinical experience with fetal surgery for a variety of life-threatening fetal anatomic defects.

Michael R. Harrison, M.D., *and N. Scott Adzick,* M.D.
San Francisco, California

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Michael T. Longaker, M.D., Ernie S. Chiu, B.S., N. Scott Adzick, M.D., Michael Stern, D.D.S., Michael R. Harrison, M.D., and Robert Stern, M.D.
San Francisco, California

Have Changing Treatment Patterns Affected Outcome for Operable Breast Cancer? Ten-year Follow-up in 1288 Patients, 1965 to 1978 297

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Hiram S. Cody III, M.D., *Edward H. Laughlin,* M.D., *Carlos Trillo,* M.D., *and Jerome A. Urban,* M.D.
New York, New York

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Max H. Cohen, M.D., PH.D., F.A.C.S., Barry J. Cohen, M.D., Jane D. Shotkin, R.N., and Paula T. Morrison, R.N.
Washington, D.C.

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Francesco Cetta, M.D.
Siena, Italy

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Marisa Lawrence, M.D., and Man H. Shiu, M.D.
New York, New York

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Gene D. Branum, M.D., Bert A. Bowers, M.D., Christopher R. Watters, M.D., Jon Haebig, PH.D., Giovanni Cucchiaro, M.D., Marwan Farouk, M.B., CH.B., F.R.C.S., and William C. Meyers, M.D.
Durham, North Carolina

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Isto H. Nordback, M.D., Jeffrey A. Clemens, M.D., Vaddappuram P. Chacko, PH.D., Jean L. Olson, M.D., and John L. Cameron, M.D., F.A.C.S.
Baltimore, Maryland

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David J. Schmeling, M.D., Keith T. Oldham, M.D., Karen S. Guice, M.D., Robin G. Kunkel, M.S., and Kent J. Johnson, M.D.
Ann Arbor, Michigan

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Charles S. Roberts, M.D., and William C. Roberts, M.D.
Bethesda, Maryland

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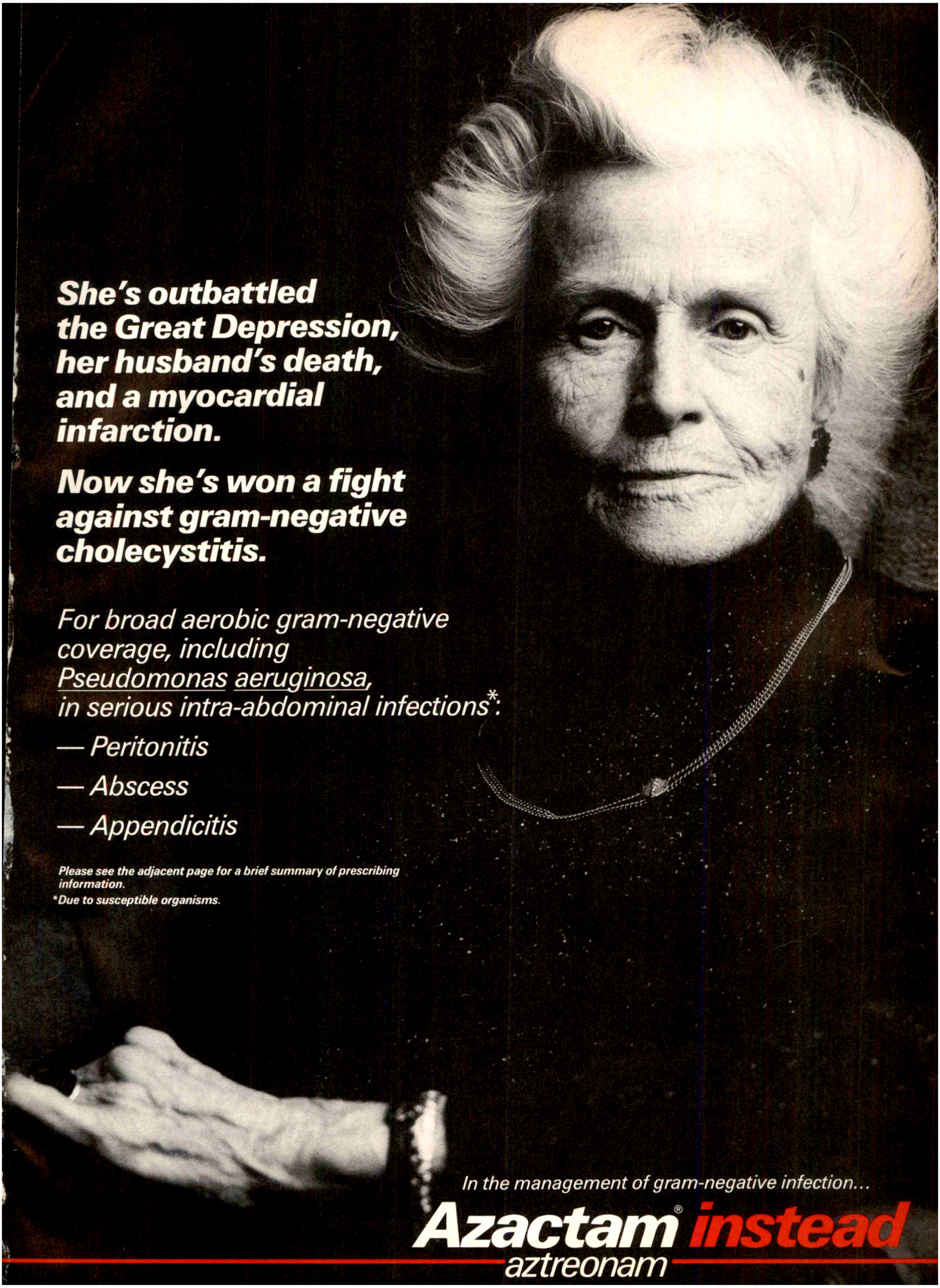

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DESCRIPTION–AZACTAM (aztreonam, Squibb) is the first member of a new class of antibiotics classified as monobactams. AZACTAM is a totally synthetic bactericidal antibiotic with activity against a wide spectrum of gram-negative aerobic pathogens. The monobactams, having a unique monocyclic beta-lactam nucleus, are structurally different from other beta-lactam antibiotics.

AZACTAM For Injection is a sterile, nonpyrogenic, sodium-free, white to yellowish-white lyophilized cake, containing approximately 780 mg arginine per gram of aztreonam for intramuscular or intravenous use following constitution. Aqueous solutions of the product have a pH in the range of 4.5-7.5.

INDICATIONS AND USAGE–Before initiating treatment with AZACTAM, appropriate specimens should be obtained for isolation of the causative organism(s) and for determination of susceptibility to aztreonam. Treatment with AZACTAM may be started empirically before results of the susceptibility testing are available; subsequently, appropriate antibiotic therapy should be continued.

AZACTAM For Injection is indicated for the treatment of the following infections caused by susceptible gram-negative microorganisms: **Urinary Tract Infections** (complicated and uncomplicated), including pyelonephritis and cystitis (initial and recurrent) caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Enterobacter cloacae, Klebsiella oxytoca*, Citrobacter* species* and *Serratia marcescens**. **Lower Respiratory Tract Infections,** including pneumonia and bronchitis caused by *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Haemophilus influenzae, Proteus mirabilis, Enterobacter* species and *Serratia marcescens**. **Septicemia** caused by *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis*, Serratia marcescens** and *Enterobacter* species. **Skin and Skin-Structure Infections,** including those associated with postoperative wounds, ulcers and burns caused by *Escherichia coli, Proteus mirabilis, Serratia marcescens, Enterobacter* species, *Pseudomonas aeruginosa, Klebsiella pneumoniae,* and *Citrobacter* species*. **Intra-abdominal Infections,** including peritonitis caused by *Escherichia coli, Klebsiella* species, including *K. pneumoniae, Enterobacter* species including *E. cloacae*, Pseudomonas aeruginosa, Citrobacter* species* including *C. freundii** and *Serratia* species* including *S. marcescens**. **Gynecologic Infections,** including endometritis and pelvic cellulitis caused by *Escherichia coli, Klebsiella pneumoniae*, Enterobacter* species* including *E. cloacae**, and *Proteus mirabilis**.

AZACTAM is indicated for adjunctive therapy to surgery in the management of infections caused by susceptible organisms, including abscesses, infections complicating hollow viscus perforations, cutaneous infections and infections of serous surfaces. AZACTAM is effective against most of the commonly encountered gram-negative aerobic pathogens seen in general surgery.

Concurrent Therapy–Concurrent initial therapy with other antimicrobial agents and AZACTAM is recommended before the causative organisms(s) is known in seriously ill patients who are also at risk of having an infection due to gram-positive aerobic pathogens. If anaerobic organisms are also suspected, therapy should be initiated using an antianaerobic agent concurrently with AZACTAM. Certain antibiotics (e.g., cefoxitin, imipenem) may induce high levels of beta-lactamase *in vitro* in some gram-negative aerobes such as *Enterobacter* and *Pseudomonas* species, resulting in antagonism to many beta-lactam antibiotics including aztreonam. These *in vitro* findings suggest that such beta-lactamase inducing antibiotics not be used concurrently with aztreonam. Following identification and susceptibility testing, appropriate antibiotic therapy should be continued.

CONTRAINDICATIONS–Aztreonam is contraindicated in patients with known allergy to this antibiotic.

WARNINGS–Pseudomembranous colitis has been reported with nearly all antibacterial agents, including aztreonam, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an oral antibacterial drug effective against *C. difficile* (e.g., vancomycin). Careful inquiry should be made for a history of hypersensitivity reaction to any antibiotic or other drugs. Antibiotics should be given with caution to any patient who has had some form of allergy, particularly to drugs. It is recommended that patients who have had immediate hypersensitivity reactions (e.g., anaphylactic or urticarial) to penicillins and/or cephalosporins should be followed with special care. If an allergic reaction to aztreonam occurs, discontinue the drug and institute supportive treatment as appropriate (e.g., maintenance of ventilation, pressor amines, antihistamines, corticosteroids). Serious hypersensitivity reactions may require epinephrine and other emergency measures.

PRECAUTIONS–General: In patients with impaired hepatic or renal function, appropriate monitoring is recommended during therapy. If an aminoglycoside is used concurrently with aztreonam, especially if high dosages of the former are used or if therapy is prolonged, renal function should be monitored because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. The use of antibiotics may promote the overgrowth of nonsusceptible organisms, including gram-positive organisms and fungi. Should superinfection occur during therapy, appropriate measures should be taken.

Carcinogenesis, Mutagenesis, Impairment of Fertility–Carcinogenicity studies in animals have not been performed. Genetic toxicology studies performed *in vivo* and *in vitro* with aztreonam in several standard laboratory models revealed no evidence of mutagenic potential at the chromosomal or gene level. Two-generation reproduction studies in rats at daily doses up to 20 times the maximum recommended human dose, prior to and during gestation and lactation, revealed no evidence of impaired fertility. There was a slightly reduced survival rate during the lactation period in the offspring of rats that received the highest dosage, but not in offspring of rats that received five times the maximum recommended human dose.

Pregnancy–Pregnancy Category B: Aztreonam crosses the placenta and enters the fetal circulation. Studies in pregnant rats and rabbits, with daily doses up to 15 and 5 times, respectively, the maximum recommended human dose, revealed no evidence of embryo- or fetotoxicity or teratogenicity. No drug induced changes were seen in any of the maternal, fetal or neonatal parameters that were monitored in rats receiving 15 times the maximum recommended human dose of aztreonam during late gestation and lactation. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, aztreonam should be used during pregnancy only if clearly needed.

Nursing Mothers–Aztreonam is excreted in breast milk in concentrations that are less than 1% of concentrations determined in simultaneously obtained maternal serum; consideration should be given to temporary discontinuation of nursing and use of formula feedings.

Pediatric Use–Safety and effectiveness have not been established in infants and children.

ADVERSE REACTIONS–Local reactions such as phlebitis/thrombophlebitis following IV administration, and discomfort/swelling at the injection site following IM administration occurred at rates of approximately 1.9% and 2.4%, respectively. Systemic reactions (considered to be related to therapy or of uncertain etiology) occurring at an incidence of 1 to 1.3% include diarrhea, nausea and/or vomiting, and rash. Reactions occurring at an incidence of less than 1% are listed within each body system in order of decreasing severity: *Hypersensitivity*–anaphylaxis. *Hematologic*–pancytopenia, neutropenia, thrombocytopenia, anemia, leukocytosis, thrombocytosis. *Gastrointestinal*–abdominal cramps; rare cases of *C. difficile*-associated diarrhea, including pseudomembranous colitis, or gastrointestinal bleeding have been reported. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS). *Dermatologic*–purpura, erythema multiforme, urticaria, exfoliative dermatitis, petechiae, pruritus, diaphoresis. *Cardiovascular*–hypotension, transient ECG changes (ventricular bigeminy and PVC). *Respiratory*–one patient experienced flushing, chest pain, and dyspnea. *Hepatobiliary*–hepatitis, jaundice. *Nervous System*–seizure, confusion, vertigo, paresthesia, insomnia, dizziness. *Musculoskeletal*–muscular aches. *Special Senses*–tinnitus, diplopia, mouth ulcer, altered taste, numb tongue, sneezing and nasal congestion, halitosis. *Other*–vaginal candidiasis, vaginitis, breast tenderness. *Body as a Whole*–weakness, headache, fever, malaise.

Adverse Laboratory Changes–Those reported without regard to drug relationship during clinical trials were: *Hepatic*–elevations of AST (SGOT), ALT (SGPT), and alkaline phosphatase; signs or symptoms of hepatobiliary dysfunction occurred in less than 1% of recipients (see above). *Hemic*–increases in prothrombin and partial thromboplastin times, eosinophilia, positive Coombs test. *Renal*–increases in serum creatinine.

OVERDOSAGE–If necessary, aztreonam may be cleared from the serum by hemodialysis and/or peritoneal dialysis.

DOSAGE AND ADMINISTRATION–Dosage adjustments are recommended for patients with impaired renal function. In elderly patients, estimates of creatinine clearance should be obtained and appropriate dosage modifications made if necessary.

HOW SUPPLIED–AZACTAM For Injection (Aztreonam For Injection)–Lyophilized–is supplied in single-dose 15 mL vials containing **500 mg,** or **1 g**/vial; in single-dose 30 mL vials containing **2 g**/vial; and in single-dose 100 mL intravenous infusion bottles containing **500 mg** or **1 g** or **2 g**/bottle.

Consult package insert before prescribing AZACTAM (aztreonam). (J4-231C)

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*Efficacy for this organism in this organ system was studied in fewer than ten infections.

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Long-term Results of Coronary Bypass Surgery: Analysis of 1698 Patients Followed 15 to 20 Years **377**

At 20 years of follow-up, 93% of patients were asymptomatic or improved after surgery and 75% had one or more patent grafts. The major determinants of survival were age, extent of coronary disease, ventricular quality, preoperative stroke, or congestive failure.

Gerald M. Lawrie, M.D., George C. Morris, Jr., M.D., and Nan Earle, B.S.
Houston, Texas

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James E. Lowe, M.D., Paul J. Hendry, M.D., Steven C. Hendrickson, M.D., and Randall Wells, B.S.
Durham, North Carolina

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Walter H. Merrill, M.D., William H. Frist, M.D., James R. Stewart, M.D., Robert J. Boucek, M.D.,
Debra A. Dodd, M.D., Theodore E. Eastburn, M.D., and Harvey W. Bender, Jr., M.D.
Nashville, Tennessee

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Gainesville, Florida

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B. Mark Evers, M.D., Stephen C. Hurlbut, M.D., Stephen K. Tyring, M.D., PH.D.,
Courtney M. Townsend, Jr., M.D., Tatsuo Uchida, B.S., and James C. Thompson, M.D.
Galveston, Texas

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E. Stanley Crawford, M.D., *Kenneth R. Hess,* M.S., *Evan S. Cohen,* M.D., *Joseph S. Coselli,* M.D., *and Hazim J. Safi,* M.D.
Houston, Texas

The Influence of Severity of Spinal Cord Ischemia in the Etiology of Delayed-onset Paraplegia 427

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William M. Moore, Jr., M.D., *and Larry H. Hollier,* M.D., F.A.C.S.
New Orleans, Louisiana

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William H. Edwards, M.D., *John A. Morris, Jr.,* M.D., *Judith M. Jenkins,* R.N., M.S.N., *Sue M. Bass,* SC.M., *and Ellen J. MacKenzie,* PH.D.
Nashville, Tennessee; and Baltimore, Maryland

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M. Kathleen Reilly, PH.D. M.D., *Malcolm O. Perry,* M.D., *and Lillian B. Nanney,* PH.D.
Nashville, Tennessee

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Richard H. Dean, M.D., *Reid W. Tribble,* M.D., *Kimberley J. Hansen,* M.D., *Elizabeth O'Neil,* M.D., *Timothy E. Craven,* M.S.P.H., *and John F. Redding II,* B.S.
Winston-Salem, North Carolina

Femoral–Distal Bypass with *In Situ* Greater Saphenous Vein: Long-term Results Using the Mills Valvulotome 457

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Magruder C. Donaldson, M.D., *John A. Mannick,* M.D., *and Anthony D. Whittemore,* M.D.
Boston, Massachusetts

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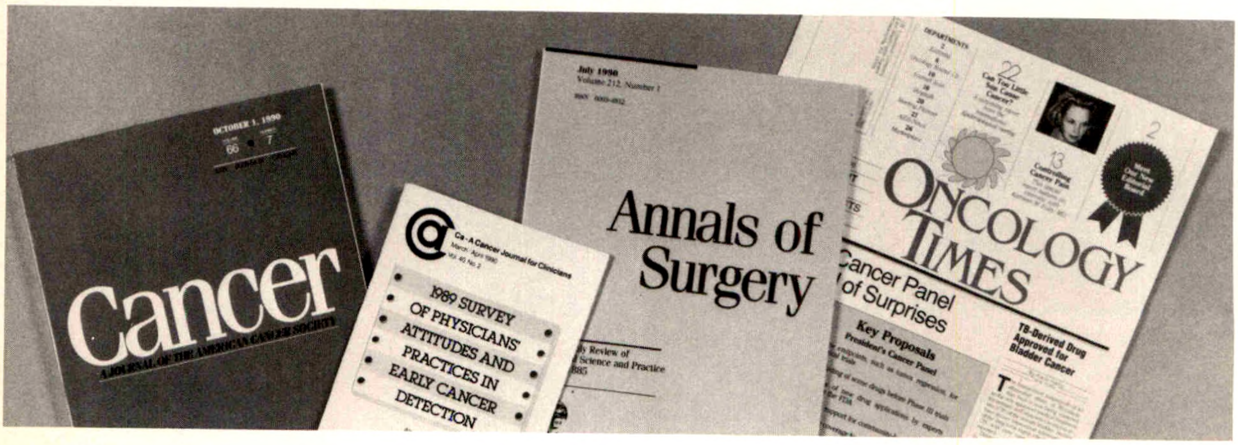
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The Fetus as a Patient

Drs. Harrison and Adzick should be commended for their pioneering efforts in the field of fetal investigation and intervention. Where all of this research and that of others will lead is anyone's guess, but society will be the better for it.

Already we have begun to realize the benefits of fetal research: perinatology is now recognized as a valid field of medical endeavor as we now see the maternal/fetal complex emphasized together rather than treated as two separate entities. Anesthesia, radiology, and pediatric surgery have joined the team as well. Clinically the main advantage of fetal monitoring to this point has been the referral of high-risk mothers known to have fetuses with correctable anomalies to centers where the best care could be provided to both mother and infant and at the optimal time. In fact this may continue to be the main advantage of such fetal monitoring programs, particularly in the case of complex congenital heart disease.

Scientifically our knowledge of fetal development and physiology has been enriched enormously by investigations such as those reported by Harrison and colleagues. In addition the best is yet to come. Even if fetal intervention eventually is limited, the knowledge will be useful to our understanding of maternal–fetal interaction, the timing of and influences on fetal organ development, development of the immune system, and a host of other issues. We have an opportunity to increase knowledge in the developing fields of molecular biology, genetics, immunology, and oncogenesis with this controllable model of serial cellular development.

Dr. Harrison and colleagues have been extraordinarily careful to admonish readers that there is much to be learned before fetal intervention becomes commonplace. Fetal intervention must be based on a firm understanding of the basic physiology and developmental biology involved in each individual case. Already we have seen far too many fetal complications produced by procedures on the fetus when intervention would not be expected to be of help anyhow in the light of present knowledge. Only medical centers with the full clinical and research capabilities similar to those in San Francisco should undertake this enterprise. Even the latter group have been slow and responsible in their application of laboratory investigation to clinical use, and others should do the same.

The perinatology group at the University of California in San Francisco has more than 20 years experience in fetal research. The members of this team appear to have identified safe anesthetic and operative management of the mother and to have determined how to operate on the uterus so it will heal and support later pregnancy and how to preserve fertility. What is yet to be learned is how to avoid fetal distress to the mother who has placentomegaly, the so-called 'mirror syndrome.' The answer to the latter question will be valuable to all pregnant mothers.

The authors have posed more questions than they have answered. Also it is likely that the lamb laboratory model does not completely mimic abnormal fetal development, which starts at the onset of gestation. Careful clinical study will be critical to a complete understanding of these issues. For example they state that in fetal hydronephrosis, intervention is only reasonable if renal and pulmonary development are threatened. While they indicate that 24 to 30 weeks is a reasonable interval for intervention, the most successful time to correct urinary obstruction in light of pulmonary development may be as early as 16 weeks. In fact their experience with patients in the urinary obstructive category suggests that diagnosis must be early enough to be effective. Consequently, not only the severity of the anomaly must be considered but the appropriate timing of intervention as well. Another consideration is that we know that many infants with bilateral hydronephrosis resolve spontaneously; their mothers do not have oligohydramnios, so Dr. Harrison's criterion is important in this regard. Another point that should not be missed is that this group screened 200 patients with urinary tract obstruction, intervened on seven patients, and had three reasonable outcomes.

The authors' experience with congenital diaphragmatic hernia is encouraging because we seem to be at the limit of what we can do for critically ill infants with this anomaly, even with extracorporeal membrane oxygenation when there is true pulmonary hypoplasia. In highly selected instances in fetuses without associated anomalies, if intervention is early enough, survival is possible.

The principles of early detection and serial imaging and recognition of fetal hydrops and maternal placentomegaly also appear to apply to the problems of chylothorax, sacrococcygeal teratoma, pulmonary cystic adenomatoid malformation, and cystic hygroma if intervention is to be considered. More basic information will be needed before it will be possible to determine if intervention is appropriate, what the appropriate selection criteria are, and what the timing of intervention should be.

In the background of this high-tech surgical enterprise lie two important social issues. The first relates to the fact that too many centers perform fetal intervention inappropriately, with unfortunate maternal and fetal morbidity, even when such intervention is unwarranted. Most centers would be better to refer their patients for now or to do nothing at all.

The second social issue is an important question related to the future of health care in America. In this time of budgetary restriction and even some rationing of health care, can we afford to support operative intervention on the fetus? Is it even socially responsible considering the larger issues of our day? By the year 2000, one third of our children will lie below the poverty level, and we must support them to ensure the future of our nation. We are having difficulties supporting our trauma centers as well. Perhaps it is reasonable and even important to continue these investigative efforts if we are ever to get the human data we cannot get from laboratory experiments. Only time will tell, but in the meantime, society has much to benefit from the information pioneers such as Dr. Harrison and his colleagues are generating.

JAMES A. O'NEILL, JR., M.D.
Philadelphia, Pennsylvania

The Fetus as a Patient

Surgical Considerations

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From the Fetal Treatment Program and the Department of Surgery, University of California, San Francisco, California

The diagnosis and treatment of human fetal defects has evolved rapidly over the past decade due to improved fetal imaging techniques and better understanding of fetal pathophysiology derived from animal models. The detection of a fetal anomaly may now lead to a change in the timing of delivery, a change in the mode of delivery, or prenatal treatment. Because most therapeutic maneuvers involve some risk to the fetus and mother, there must be a reasonable expectation that the procedure is feasible, safe, and effective before it can be attempted in humans. This requires reliable information about the pathophysiology and natural history of the disease process, the efficacy of fetal surgical intervention in ameliorating the disease, and the feasibility and safety of the proposed intervention. This paper focuses on the rationale and initial clinical experience with fetal surgery for a variety of life-threatening fetal anatomic defects.

PRENTAL DIAGNOSIS HAS undergone an explosion of growth in the past decade. The primary impetus for this rapid expansion has come from the widespread use of prenatal ultrasonography. After the first reports of *in utero* ultrasonographic diagnosis of congenital anomalies in the 1970s, increasingly sophisticated equipment and experience in interpretation led to the accurate prenatal diagnosis of a growing number of surgical lesions.[1]

Prenatal diagnosis and serial sonographic study of fetuses with anatomic lesions now makes it possible to define the natural history of these abnormalities, determine the pathophysiologic features that affect clinical outcome, and formulate management based on prognosis. Prenatal diagnosis has defined a 'hidden mortality' for some lesions such as congenital diaphragmatic hernia, bilateral hydronephrosis, sacrococcygeal teratoma, and cystic adenomatoid malformation of the lung. These lesions, when first evaluated and treated after birth, demonstrate a favorable selection bias. The most severely affected fetuses often die *in utero* or immediately after birth.[2]

Routine obstetric sonography changed the surgical management of many congenital anomalies. Most correctable malformations that can be diagnosed *in utero* are best managed by appropriate medical and surgical therapy after maternal transport and planned delivery at term. Prenatal diagnosis may influence the timing (Table 1) or the mode (Table 2) of delivery. In rare cases, various forms of *in utero* therapy may be possible either now or in the future (Table 3). For instance hematopoietic stem cell and hepatic enzyme deficiencies may be treated by *in utero* stem cell and hepatocyte transplantation in the near future.[3]

The possibility of open fetal surgical intervention, although a formidable undertaking, may be the only solution for some fetal problems. Fetal surgery is only justifiable, however, if (1) the natural history and pathophysiology of the disease is well understood; (2) the prenatal diagnosis is accurate, capable of excluding other anomalies, and able to predict which fetuses have a sufficiently bad prognosis to justify *in utero* intervention; (3) if *in utero* correction is shown to be efficacious in animal models; and (4) if maternal risk is proved to be acceptably low.

In the past decade, we investigated the rationale and feasibility of *in utero* repair for a number of fetal anomalies, including congenital hydronephrosis, congenital diaphragmatic hernia, sacrococcygeal teratoma, cystic adenomatoid malformation, chylothorax, and simple types of congenital heart disease. In addition some recent experimental studies delineating the ability of the fetus to heal without scarring may have implications for all surgeons.[4–6] This review will focus on our experimental and clinical experience with open fetal surgery for prenatally diagnosed life-threatening anatomic anomalies.

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TABLE 1. *Defects that May Lead to Induced Preterm Delivery for Early Correction* Ex Utero

- Obstructive hydronephrosis
- Gastroschisis or ruptured omphalocele
- Intestinal ischemia and necrosis secondary to volvulus, meconium ileus, and so on
- Amniotic band malformation complex

Management of the Fetus with Congenital Hydronephrosis

Unrelieved urinary tract obstruction interferes with fetal development. The severity of damage at birth depends on the type, degree, and duration of the obstruction.[7,8] Although children born with partial bilateral obstruction may have only mild hydronephrosis that is reversible with decompression after birth, children born at term with high-grade obstruction may already have advanced hydronephrosis and renal dysplasia that is incompatible with life. In addition oligohydramnios secondary to decreased fetal urine output produces pulmonary hypoplasia, which often is fatal at birth.

It is possible that the life-threatening problems of respiratory and renal insufficiency may be ameliorated if the obstruction is relieved early enough in gestation to allow normal development to proceed. Optimal clinical management of both patients, mother and fetus, depends on a thorough understanding of the pathophysiology of fetal obstructive uropathy and its sequelae on the developing fetus.

The approach to fetal hydronephrosis developed in the last decade is a paradigm for fetal treatment in general. In this short period, the management of fetal hydronephrosis advanced dramatically due to multiple studies defining the natural history and pathophysiology of fetal urinary tract obstruction and to an intensive search for ways to assess fetal renal function and improve selection for treatment. From this large body of experimental and clinical work, for any individual case, the family can be counseled about the prognosis and options in management, ranging from termination of a hopeless pregnancy to prenatal intervention for those few fetuses whose renal and pulmonary development is threatened.

Development of the Fetal Lamb Model

To study the pathophysiology of fetal urethral obstruction and the efficacy and feasibility of correction *in utero*, it was necessary first to develop an animal model. Studies using fetal lambs evaluated the effect of obstruction and its subsequent correction on pulmonary and renal development.[9,10] We produced an accurate model of severe bilateral hydronephrosis in the fetal lamb by ligating the urachus and occluding the urethra with an ameroid constrictor or a ligature at 95 to 105 days gestation (full term is 145 days). Then we decompressed some of the obstructed fetuses by performing a suprapubic cystostomy at a second fetal operation about 3 weeks later and compared obstructed, decompressed, and control lambs at birth (Fig. 1). Uncorrected lambs did poorly; one half of them were stillborn. Liveborn obstructed lambs had severe respiratory insufficiency and only one survived the newborn period. The lungs were hypoplastic by weight and volume compared to corrected animals. The bladder, ureters, and renal pelves were dilated severely, mimicking the morphologic disease in human neonates. In contrast, the corrected lambs fared much better. Seven of nine lambs diverted *in utero* were liveborn, with resolution of the urinary tract dilatation and with far less respiratory difficulty. Relatively late obstruction in the fetal lamb (100 days), however, did not produce the typical cystic and dysplastic changes seen in human urinary tract malformations. To address the relationship between obstruction and renal dysplasia, an earlier gestational model was developed.

To test whether obstruction earlier in fetal life leads to renal dysplasia, we produced complete unilateral ureteral obstruction in fetal lambs at the beginning of the second trimester (55 to 65 days gestation). We documented that the kidney obstructed at this early stage was both hydronephrotic with ureteral and calyceal dilation proximal to the ligation, and dysplastic when examined at term.[11] This model then was used to determine whether renal dysplasia associated with fetal urinary tract obstruction was preventable by *in utero* decompression.

Following early second trimester unilateral ureteral ligation in 25 fetal lambs, the fetuses underwent reoperation and ureterostomy of the obstructed ureter after three predetermined time intervals (3, 6, or 9 weeks).[12] The fetus was returned to the uterus and subsequently delivered at term by Cesarean section. Each newborn had the function and morphology of the previously obstructed kidney compared to the contralateral control kidney. This study demonstrated that ureteral obstruction in the early midtrimester with subsequent decompression before term prevented renal dysplasia. Urinary tract decompression reversed the obstructive changes and the degree of pathologic and functional impairment seen in the obstructed kidney was proportional to the duration of obstruction. Other studies in fetal lambs have shown that the oligohydramnios-induced pulmonary hypoplasia associated with obstructive uropathy is similar to that seen in human

TABLE 2. *Defects that May Lead to Cesarean Delivery*

- Giant omphalocele
- Large sacrococcygeal teratoma, cervical hygroma, cervical teratoma
- Malformations requiring preterm delivery in the presence of inadequate labor or fetal distress

TABLE 3. *Defects That May Require* In Utero *Treatment*

Malformation	Effect on Development	*In Utero* Treatment
Urethral obstruction	Hydronephrosis, lung hypoplasia → renal, respiratory failure	Vesicostomy
Congenital diaphragmatic hernia	Pulmonary hypoplasia → respiratory failure	CDH closure
Fetal chylothorax	Pulmonary hypoplasia → respiratory failure	Thoracoamniotic shunt
Sacrococcygeal teratoma	Massive arterio-venous shunting → placentomegaly, hydrops	Excision
Cystic adenomatoid malformation of the lung	Pulmonary hypoplasia, hydrops	Excision

fetuses and that decompression of the obstructed urinary tract permits restoration of amniotic fluid volume and compensatory lung growth.[13,14]

There are several lines of evidence that suggest that pulmonary hypoplasia is the result of simple compression of the fetal lung.[15–17] In cases of congenital hydronephrosis, the massively distended urinary tract elevates the diaphragm and the oligohydramnios results in a small intrauterine cavity that compresses the fetal thorax. If the lung changes are secondary to compression and are not due to a primary pulmonary malformation, restoration of normal amniotic fluid volume by fetal urinary tract decompression would reverse the constraint on normal lung growth. The lamb studies support this hypothesis. Lambs born after correction of urinary tract obstruction *in utero* fared much better, and the improvement correlated roughly with larger lungs. In addition we demonstrated in a fetal rabbit model that decompressing the lungs by restoration of amniotic fluid volume or by reducing pressure on the diaphragm allows the lungs to grow.[18] Further studies in the same experimental preparation suggest that the loss of the internal stenting force of fetal lung fluid is an important etiologic factor.[19]

The Problem of Selection: Assessment of Fetal Renal Function

A major problem in management of the fetus with hydronephrosis is determining how to select from a large number of fetuses with dilated urinary tracts only those with obstruction severe enough to compromise renal and pulmonary function at birth, yet not so severe that renal function cannot be salvaged even with *in utero* decompression. The fetus with a dilated low-pressure system who continues to have good urine output and adequate amniotic fluid volume requires no intervention. At the other end of the spectrum, the fetus with severe renal dysplasia that is not reversible; even with decompression, clearly should not be treated. The fetus with unilateral disease of any type with a normally functioning contralateral kidney can be managed conservatively because the disease is not life threatening. But the fetus with bilateral

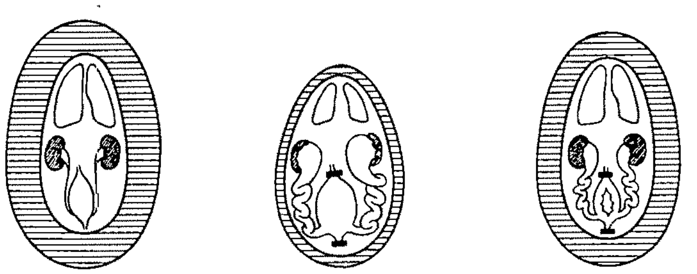

FIG. 1. Summary of data. Obstructed lambs had a high mortality rate, small lungs, and grossly dilated urinary tracts. Decompression *in utero* significantly improved survival, lung size, and urinary tract dilation. Four obstructed lambs and two decompressed lambs were delivered vaginally before planned ceasarean delivery, so viability could not be assessed (reprinted with permission).

	Controls (n=8)	**Obstructed (n=8)**	**Obstructed, decompressed (cystostomy) (n=9)**
Viability	8/8	1/4 (w/resp. distress)	7/7 (w/resp. distress)
(Stillborn)	0	4	2
Urinary tract dilatation	none	2+ to 4+	1+ to 2+
Lung wt./body wt. % ± S.D.	3.03 ± 0.90	1.85 ± 0.46	2.61 ± 0.48
Air cap./body wt. % ± S.D.	5.64 ± 2.07	2.59 ± 0.76	4.34 ± 1.26

hydronephrosis and unknown renal functional potential who might be a candidate for intervention requires renal function assessment.

The presence of oligohydramnios is a critical determinant of death.[20] Fetuses identified with oligohydramnios in the early second trimester have a mortality rate in excess of 90%.[21,22] We tried to define criteria to predict which of these fetuses would be salvageable. To be a candidate for fetal intervention, the affected fetus must have good residual renal function at the time of diagnosis, despite oligohydramnios. The ultrasound appearance of the fetal kidneys provides valuable prognostic information if the renal parenchyma shows increased echogenicity or cystic changes, but is less predictive in their absence.[23]

We reviewed our experience with 20 fetuses with congenital bilateral hydronephrosis referred for treatment to determine the prognostic value of various criteria used to assess renal functional potential.[24] Based on these results, six prognostic criteria to identify the fetus with 'good function' and 'poor function' were generated (Table 4). Although these results are based on a retrospective analysis, the utility of these parameters was confirmed in recent prospective and retrospective studies.[21,22] The development of prognostic criteria that predict the potential for recovery greatly simplified counseling of the families and selection of appropriate management. The prognostic criteria (urine Na <100 mEq/L, Cl <90 mEq/L, Osm <210 mosm, and normal fetal kidneys by ultrasound) have proved to predict reliably neonatal and long-term outcome after *in utero* urinary tract decompression, and the urine studies can be obtained by a single fetal bladder aspiration under ultrasound guidance.

An Algorithm for Management

From our cumulative clinical and laboratory experience, we derived the following general guidelines for management of the fetus with hydronephrosis (Fig. 2). Initial evaluation should begin with an ultrasound to confirm the diagnosis, the anatomic level of obstruction, the status of the amniotic fluid, and the presence of associated anomalies. If an associated life-threatening anomaly is present, the family should be counseled and allowed to choose expectant management or termination of the pregnancy. If hydronephrosis appears to be an isolated defect and the amniotic fluid volume is adequate, the mother should be followed by serial ultrasound. If amniotic fluid volume remains adequate, then the mother should receive routine obstetric care, and the fetus can be treated after birth. If moderate-to-severe oligohydramnios develops, the fetus should undergo a complete prognostic evaluation to determine the fetus's potential for normal renal and pulmonary function at birth. For the fetus with predicted renal dysplasia, aggressive obstetric care or *in utero* decompression is not indicated. For the fetus with predicted preserved renal function, there are two management options depending on fetal lung maturity. For the fetus with mature lungs, immediate delivery and *ex utero* decompression is indicated, and for the fetus with immature lungs, *in utero* decompression is recommended. For open fetal surgery, the gestational age at diagnosis should be less than 28 weeks, as successful decompression sometimes can be performed after this time with a percutaneously placed fetal vesicoamniotic shunt catheter. Before 28 weeks gestation, fetal catheter placement has been unsuccessful largely due to frequent catheter obstruction and dislodgement.[25]

TABLE 4. *Prognostic Criteria for the Fetus with Bilateral Obstructive Uropathy: Fetal Urine Composition and Volume*

Predicted Function	Sodium (mEq/mL)	Chloride (mEq/mL)	Osmolarity mosmol	Output (mL/hr)
Poor	>100	>90	>210	<2
Good	<100	<90	<210	>2

The Evolution of Open Fetal Surgery for Hydronephrosis

The criteria for attempting open fetal surgery were satisfied by our group in the early 1980s. The first open case for hydronephrosis was performed in 1981,[26] and six others have been performed since then. It is important to remember that only 7 of more than 200 cases of bilateral hydronephrosis referred for management during the last decade were deemed appropriate for open fetal surgery.[25,27] The first fetus had bilateral ureterostomies and the subsequent six had marsupialization of the bladder at 18 to 24 weeks gestation. The first five pregnancies proceeded to Cesarean delivery at 32 to 35 weeks gestation. The sixth fetus never drained urine well after vesicostomy and was removed at reexploration by the parent's request because of a severe cloacal anomaly. The seventh fetus underwent successful urinary tract decompression but subsequently died 2 weeks later from pulmonary hypoplasia. This baby was delivered prematurely as a result of the mother's discontinuing her oral tocolytic therapy.

Three fetuses had prolonged return of normal amniotic fluid dynamics and all three had adequate pulmonary function at birth, suggesting that fatal pulmonary hypoplasia associated with early severe oligohydramnios had been reversed. Two other neonates died at birth with pulmonary hypoplasia. One had no amniotic fluid even after decompression due to our inability to predict fetal renal function early in our experience. The other had some amniotic fluid after decompression but a tiny chest cavity due to a long period of severe oligohydramnios before decompression. Of the three surviving infants, one had normal renal function when she died of unrelated causes

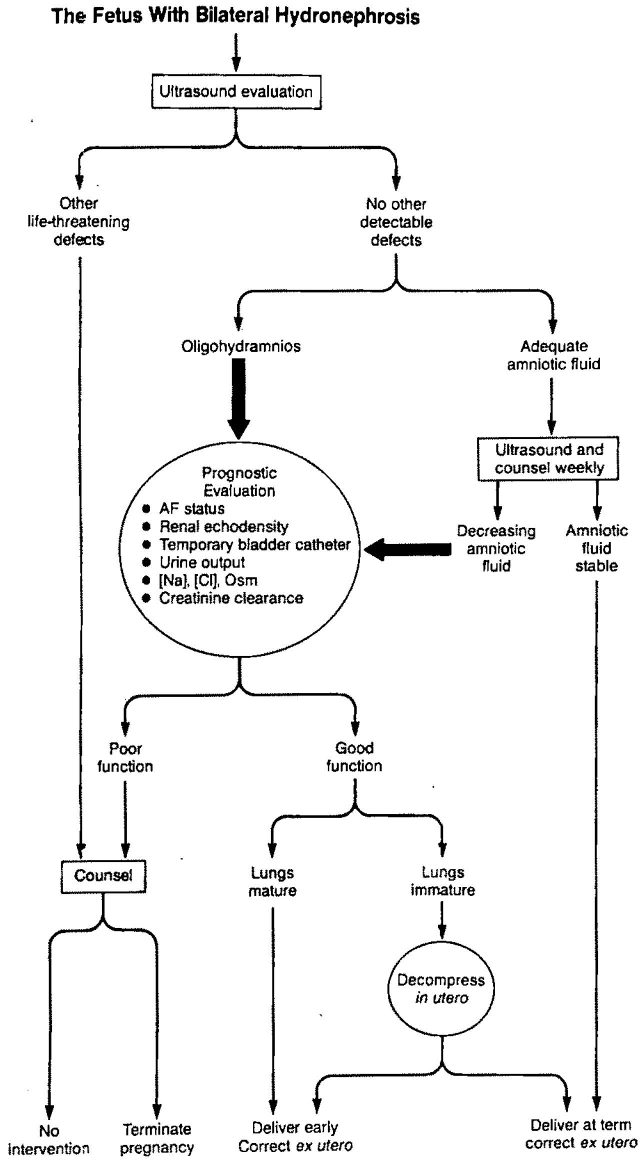

FIG. 2. Management scheme for the fetus with bilateral hydronephrosis.

at 9 months of age. One has normal renal function at age 3 years. The third developed failing renal function by 3 years, has grown and developed normally, and subsequently received a successful kidney transplant. Our current selection criteria would accurately exclude from treatment the two fetuses who died of pulmonary hypoplasia.

Throughout this initial period of performing fetal surgery, our selection criteria have been evolving. Improvements in selection now make it possible to avoid intervention in hopeless cases. This small series of human cases confirms that the development of fatal pulmonary hypoplasia can be prevented if amniotic fluid dynamics can be restored by decompression of the obstructed urinary tract. It is still unclear if *in utero* intervention arrested or reversed cystic dysplastic changes caused by obstructive uropathy because it is possible that the dysplastic changes initiated *in utero* will compromise renal function progressively as functional demand increases with growth. We believe, however, that relief of obstruction during the most active phase of nephrogenesis, between 20 and 30 weeks gestation, may obviate further damage and allow nephrogenesis to proceed normally.[24] Further experience and long-term follow-up are necessary to determine the effectiveness of *in utero* decompression in reversing or arresting renal damage caused by obstruction.

Management of the Fetus with Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) is an anatomically simple defect that is correctable easily by removing the herniated viscera from the chest and closing the diaphragm.[28] However many infants with CDH die of pulmonary insufficiency despite optimal postnatal care because their lungs are too hypoplastic to support extrauterine life. The pulmonary hypoplasia seen with CDH has been well documented clinically and experimentally; it appears to be caused by compression of the developing fetal lung by herniated bowel. In this section, the evolution of *in utero* therapy for CDH will be described. As was the case for bilateral hydronephrosis, 10 years of experimental and clinical work that supports the pathophysiologic rationale for correction of CDH *in utero* will be reviewed.

The Fetal Lamb Model

To study the pulmonary hypoplasia that accompanies CDH and the possibility of reversing these changes by correcting the CDH *in utero*, a model was developed in which a conical, silicone-rubber balloon was inflated progressively in the left hemithorax of fetal lambs over the last trimester to simulate compression of the growing fetal lung by abdominal viscera.[29] Lambs with inflated intrathoracic balloons deteriorated rapidly at term delivery and died of respiratory insufficiency despite maximal resuscitation and ventilatory support. Deflation of the balloon midway through the third trimester (simulated 'correction') allowed sufficient lung growth to alleviate respiratory insufficiency and to assure survival in five of five lambs delivered by Cesarean section.[30] Simulated correction produced a significant increase in lung weight, air capacity, compliance, and area of the pulmonary vascular bed (Fig. 3).

Although the balloon model established the efficacy of *in utero* repair, it could not be used to study the feasibility of correction or to develop the surgical techniques necessary for actual successful fetal surgical repair. For this purpose we had to create and then attempt to repair surgically actual fetal diaphragmatic hernias. We created

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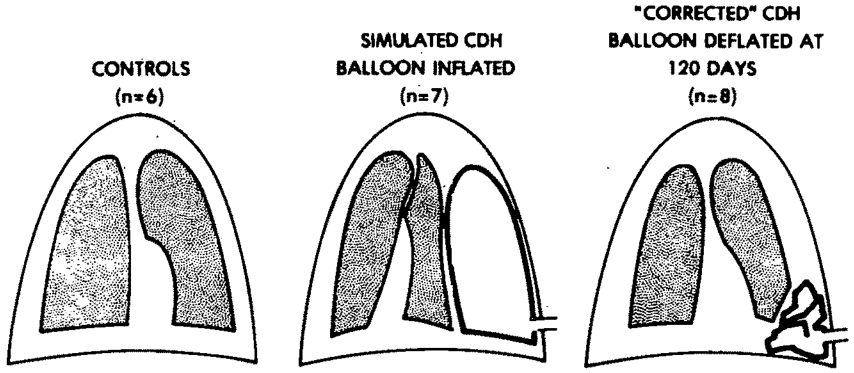
diaphragmatic hernias in fetal lambs by making a hole in the left diaphragm and demonstrated that herniated viscera produced pulmonary hypoplasia comparable to that produced by the balloon. We then tried to repair the CDH surgically at a second operation.[31]

The first attempts at repair were unsuccessful because increased intra-abdominal pressure secondary to replacement of the viscera into the abdomen resulted in severely compromised umbilical venous blood flow. It became clear that the abdominal cavity would need to be enlarged to prevent increased intra-abdominal pressure after CDH repair. Incorporating a piece of silastic into the abdominal wall proved to be a satisfactory solution allowing the abdominal contents to be accommodated without increased pressure. When we used these techniques for repair of fetal CDH, the lambs survived at term and when they were killed the lungs were well expanded, histologically mature, and much larger than those of uncorrected animals.[31] These findings were confirmed by others using a similar fetal lamb model.[32] Subsequent pulmonary morphometric studies showed that an early gestational CDH lamb model simulates the morphologic features that correlate with fatal outcome for human neonates with CDH and persistent fetal circulation, and that fetal surgical repair ameliorates these vascular changes and permits compensatory lung growth and development.[33]

The Natural History of Congenital Diaphragmatic Hernia

Survey data derived from neonatal centers underestimate the incidence and mortality rate of CDH because the more severely affected infants often die before the anomaly is recognized. Minimum incidence figures derived from various sources range from 1 in 2400 to 1 in 5000 live births; the true incidence, including stillborn fetuses, is probably about 1 in 2200 births.[2,34–36] Paradoxically the mortality rate of infants with CDH reported from major neonatal centers has not improved with the recent improvements in neonatal transport and intensive care. Earlier reported series quoted mortality rates of about 50% for postnatally detected CDH but included only the most favorable cases, those that survived to be transferred to the major referral center. The most severely affected infants died before they came to the attention of the referral center, accounting for a significant 'hidden mortality,'[2] a situation directly analogous to that seen with prenatally diagnosed bilateral hydronephrosis. With improved neonatal transport and respiratory support, some of these desperately ill infants now survive long enough to be treated. Because the mortality rate is extremely high in this group, recent series from highly capable centers often show dismal results.[37]

Management of the fetus with prenatally diagnosed CDH depends on an understanding of the natural history, pathophysiology, and prognostic factors affecting outcome. It would seem that prenatal diagnosis of CDH would result in immediate postnatal repair and survival. However our initial reported experience with fetal CDH was very disappointing—there were no survivors of seven fetuses prospectively diagnosed before birth.[38] This led to a multicenter survey that documented the natural history and clinical outcome of fetal CDH in 94 cases.[39] This study demonstrated that the prenatal sonographic diagnosis was accurate, the mortality rate was high (80%), and polyhydramnios was a prenatal predictor of poor clinical outcome. A subsequent study of 38 prenatally diagnosed cases from a single medical center permitted a detailed assessment of prognostic factors and evaluation of the impact of extracorporeal membrane oxygenation (ECMO) on outcome.[40] This study found that survival was poor despite optimal postnatal therapy, including ECMO, and



VIABILITY	6/6 LIVED	6/6 DIED	5/5 LIVED (with resp. distress)
Lung Weight	123.2±25.4	49.6±6.6	79.1±6.0
Lung Wt./Body Wt.	3.42±0.30	1.71±.03	2.26±.14
Air Capacity	222.5±47.9	58.8±7.6	151±10.0
Air Cap./Body Wt.	6.24±0.84	2.37±0.12	4.55±0.32

FIG. 3. Summary of data for lambs with simulated CDH (reprinted with permission).

that both polyhydramnios and an early gestational diagnosis were associated with a dismal outcome. Thus the severity of a fetal CDH can be judged by the timing of herniation, the degree of pulmonary compression (lung-to-thorax ratio at the level of a four chamber view of the heart), and the presence of polyhydramnios.

Initial Experience with Repair In Utero

We obtained the approval of the Committee on Human Research in 1983 for open fetal surgery for CDH. Only eight cases in 7 years have met our stringent selection criteria. In addition it has been imperative that the families understand the risks of fetal surgery and be willing to travel to San Francisco. Finances were a major stumbling block because insurance companies refused to cover any expenses associated with this experimental procedure. Although there were no professional fees, the cost of the procedures and hospitalization had to be borne by the investigating institution. Although we were contacted by telephone about a large number of fetuses with CDH, only a fraction (less than 1 in 10) was even a candidate to come to San Francisco for further evaluation. Of the potential candidates, at least one half were excluded by social and financial considerations.

After extensive experimental work demonstrated the efficacy, feasibility, and safety of repair *in utero*, we tried to salvage eight highly selected fetuses with severe CDH by open fetal surgery.[41] The experience with these very severe cases initially was discouraging, but each of these cases contributed to invaluable knowledge and experience that eventually led to the first clinical success. The first three fetuses died at operation because attempts to reduce the friable incarcerated liver from the fetal chest were unsuccessful. In the fourth case, a Gore-Tex diaphragm was constructed around the liver but lung decompression was ineffective and the baby died at birth. The last four fetuses were repaired successfully and the technical problem with mildly herniated liver proved to be surmountable. All four demonstrated rapid growth of the lung *in utero* and had surprisingly good lung function after birth. Two subsequently died of nonpulmonary problems (an unrelated nursery accident in one and intestinal complications in the other), but the last two babies have done well.[42]

An Algorithm for Prenatal Management of CDH

Figure 4 shows our proposed algorithm for management. Once a diaphragmatic hernia is diagnosed by ultrasound, the patient should be referred for chromosomal analysis by amniocentesis (results in about 2 weeks) or percutaneous umbilical blood sampling (results in about 2 days), screening for other anatomic abnormalities by an experienced obstetric sonographer, and evaluation for cardiac abnormalities by fetal echocardiography. When associated serious anomalies are discovered, the family may choose to terminate the pregnancy.

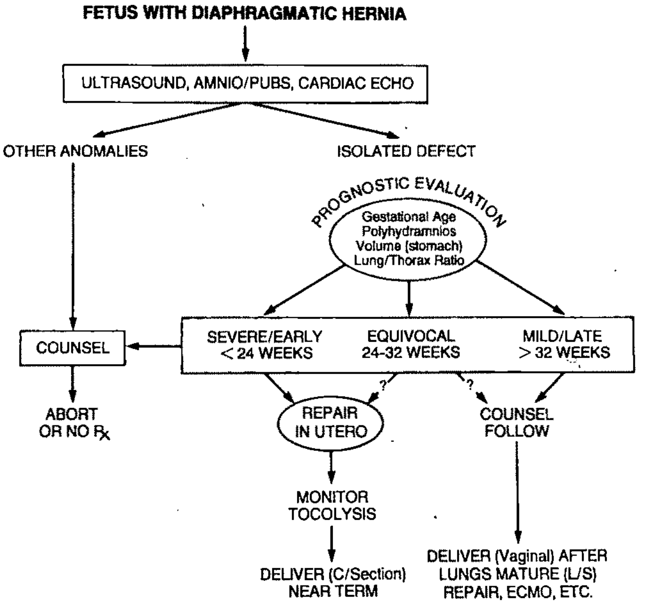


FIG. 4. Algorithm for management of the fetus with CDH (reprinted with permission).

There is a wide spectrum of severity in CDH. Some mildly affected fetuses will be detected later in gestation, develop polyhydramnios later or not at all, and have a smaller volume of viscera in the chest. These fetuses should be followed by sonogram and delivered at an appropriate tertiary perinatal center after the lungs are mature. Unfortunately most fetuses are on the severe end of the spectrum and will not survive even with optimal conventional pre- and postnatal management. In general these fetuses will be detected earlier, develop polyhydramnios earlier, and have a larger volume of viscera in the chest (dilated stomach, impressive mediastinal shift, little lung visible in either thorax). Every effort should be made to determine if the liver is herniated into the chest because this affects prognosis and the technical difficulty of repair before birth. Between 20 and 30 weeks, the family can choose between conventional management or fetal repair depending on assessment and their personal attitude. After 30 weeks the only option is conventional management aimed at maximizing postnatal care. Although fetal repair theoretically is possible until 32 weeks, it is probably best performed before 30 weeks for two reasons. First the longer the decompressed lung has to grow before it is required to support life at birth, the better (and preterm labor associated with hysterotomy may shorten the remaining gestation). Second it is our impression that the risk of inducing preterm labor is greater when the procedure is performed later in gestation. Although it would seem technically advantageous to operate on a larger fetus with more mature tissues, surgical procedures have proved feasible in fetuses as young as 18 weeks. Now we will consider fetuses between 20 and 30 weeks gestation for *in utero* repair.

Management of Fetal Chylothorax

Congenital pleural effusions often are due to fetal chylothorax (FCT) and can be diagnosed as early as 16 weeks gestation.[43] Small effusions may be harmless, while large effusions may result in pulmonary compression, pulmonary hypoplasia, and hydrops. We recently reported a series of 32 cases.[44] The overall mortality rate was 53%. Polyhydramnios was present in 22 cases and was not associated with a higher mortality rate. Early diagnosis (less than 32 weeks gestation) and hydrops were associated with a higher mortality rate. Pleural fluid was available in 12 patients, all of whom had more than 80% lymphocytes on cell count, which confirmed the diagnosis of FCT.

Small effusions diagnosed late in gestation often have a satisfactory outcome without prenatal treatment and some resolve spontaneously. In these cases, serial ultrasound examinations should be performed with appropriate postnatal follow-up. For large effusions causing hydrops, *in utero* decompression may offer the only hope for survival. Although success with repeated percutaneous thoracenteses *in utero* has been reported, we recently used a thoracoamniotic shunt to decompress successfully the FCT after multiple attempts at aspiration failed to drain permanently the fetal chest. Rodeck[45] reported the successful placement of a thoracoamniotic shunt in eight fetuses with massive FCT. Six of these infants survived, five without respiratory difficulty after birth. Lung reexpansion was seen in all of the survivors, but not in the two who died.

Management of Fetal Tumors

Sacrococcygeal Teratoma

Most babies with sacrococcygeal teratoma (SCT) are diagnosed as newborns when the malignant potential is low and the prognosis is good. However prenatal diagnosis identified fetuses with SCT who die *in utero*. The gestational age has important prognostic significance. We reported a series in which six of eight fetuses survived when the diagnosis was made after 30 weeks gestation, but only 1 of 14 fetuses survived when the diagnosis was made before 30 weeks gestation.[46] When diagnosed before 30 weeks gestation, invariably there has been development of massive tumor enlargement, fetal hydrops, and placentomegaly. In each of six fetuses diagnosed at 14 to 23 weeks gestation, the mothers developed 'mirror syndrome' with vomiting, hypertension, edema, and proteinuria. Two of the six affected mothers required treatment in the intensive care unit for pulmonary edema.

We recently demonstrated by Doppler ultrasound that the tumor in these severe cases behaves as a large arteriovenous fistula with markedly increased distal aortic blood flow and shunting of blood away from the placenta.[47] Fetal demise presumably occurs because of high-output cardiac failure with the development of hydrops.

These findings have important implications for management. Fetuses with lesions larger than 5 cm should be delivered by Cesarean section to avoid dystocia, tumor rupture, or hemorrhage into the tumor, which may occur with vaginal delivery.[46] Cases with hydrops diagnosed after 30 weeks gestation should be delivered when pulmonary maturity is attained. Lesions diagnosed before 30 weeks gestation usually have a poor outcome and may require surgical excision *in utero.*

Congenital Cystic Adenomatoid Malformation

Congenital cystic ademomatoid malformation (CCAM) can present as a fatal lesion in a fetus or neonate, or as a relatively mild lesion causing respiratory difficulty or recurrent infections in an infant or child. It represents a spectrum of disease characterized by cystic lesions of the lung. The macrocystic type has cysts that grow to several centimeters in diameter. Microcystic disease has multiple cystic lesions less than 5 mm in diameter. Prenatal ultrasound generally can distinguish individual cysts in macrocystic disease while microcystic lesions usually have the appearance of an echogenic, solid lung mass.[48]

Differences in survival rate of patients with CCAM have been ascribed previously to the histologic type of the lesion, but our experience and that of others demonstrates that an unfavorable outcome is associated most closely with hydrops. Hydrops probably is secondary to vena cava obstruction or cardiac compression from the extreme mediastinal shift caused by these lesions, and hydrops has been associated with other space-occupying thoracic lesions.[49] The invariably fatal outcome seen with large CCAM lesions is related to several factors, including development of hydrops, hypoplasia of normal lung tissue secondary to prolonged compression *in utero,* and lack of early diagnosis and immediate postnatal surgery. Macrocystic lesions may resolve spontaneously when followed by serial ultrasound throughout the course of pregnancy.[50]

It is possible that *in utero* surgical decompression or removal of the CCAM will reverse the hydrops and allow sufficient lung growth to permit survival in these severe cases. We demonstrated experimentally that *in utero* pulmonary resection is feasible and that compensatory lung growth of the opposite lung occurs.[51] Thoracentesis of macrocystic lesions *in utero* does not provide lasting decompression of normal lung tissue.[48] However percutaneous placement of a double pigtail catheter shunt between a large lung cyst and the amniotic space in a fetus with CCAM at 20 weeks gestation resulted in sustained cyst decompression and resolution of hydrops, with delivery 17 weeks later and successful postnatal surgery.[52]

Maternal Mirror Syndrome: An Unsolved Problem After Resection of Fetal Tumors

Large fetal tumors may result in placentomegaly, hydrops, and fetal death. The 'maternal mirror syndrome' (MMS) is a hyperdynamic state in which the maternal physiology 'mirrors' that of the hydropic fetus with hypertension, peripheral and pulmonary edema, and gastrointestinal and renal dysfunction. Maternal mirror syndrome is associated with severe Rh disease and other fetal conditions that cause placentomegaly and complicates control of preterm labor.[53] We encountered this syndrome twice after resection of large tumors in hydropic moribund fetuses.

The first case was a fetus at 21 weeks gestation referred with a huge sacrococcygeal teratoma, placentomegaly, and hydrops due to massive arteriovenous shunting through the tumor.[47] Successful complete resection of the tumor *in utero* led to marked improvement in the fetal hydrops. The second case was a fetus at 27 weeks gestation referred with a giant congenital cystic adenomatoid malformation with massive mediastinal shift, hydrops, and placentomegaly. A thoracoamniotic shunt was not possible because the lung lesion was microcystic. The mass was resected successfully *in utero* by right middle lobectomy with consequent improvement in the fetal pathophysiology.[54] In both cases placentomegaly persisted after operation and the mothers developed progressive MMS that prevented adequate tocolysis despite fetal improvement. A Cesarean section was performed for maternal safety in the first case after 12 days and the second case after 6 days, and the MMS resolved quickly. The premature infants died soon after delivery from respiratory insufficiency.

Although fetal tumor excision is technically feasible, reversal of the fetal pathophysiology did not rapidly correct the placentomegaly or resolve the MMS. Maternal mirror syndrome may be caused by placental release of vasoactive compounds resulting in a severe pre-eclamptic state. Until the MMS riddle is solved, earlier intervention before the onset of placentomegaly and hydrops may be the only approach to salvage these doomed fetuses.

Recently successful *in utero* resection of a large CCAM was performed in a 23-week-old fetus with ascites but no placentomegaly. After tumor resection, the ascites resolved and good lung growth occurred *in utero*. That child is thriving at 8 months of age.[54] In that case the early diagnosis, the large size of the tumor, and the early onset of hydrops indicated a dismal prognosis, which led us to consider prenatal intervention as the only hope for a successful outcome. We can now add appropriately selected cases of CCAM to the list of congenital lesions that are amenable to fetal surgical therapy.

Congenital Heart Disease

Many types of congenital cardiac disease now can be diagnosed readily *in utero* with a high degree of accuracy.[55] Prenatally diagnosed complete heart block (CHB) can occur without associated cardiac anomalies, is often refractory to attempts to increase heart rate and cardiac output by medical therapy, and results in fetal demise.[56] We developed a model of CHB in fetal lambs and have demonstrated the feasibility of epicardial ventricular or atrioventricular pacing to increase cardiac output. The model may facilitate the development of new clinical therapies to salvage refractory cases of fetal CDH.[57] Another group of investigators has tried percutaneous transthoracic pacing in a hydropic fetus with CHB, but this effort failed for technical reasons.[58]

Although the *in utero* pathophysiology of congenital cardiac lesions is not understood completely, it appears that decreased blood flow during fetal life can result in secondary hypoplasia of vessels or cardiac chambers.[59] Experimental intrauterine repair of pulmonary artery stenosis is feasible without cardiac bypass[60,61] and hypothermia or bypass techniques may make open fetal cardiac surgery possible in the future.[62,63]

Maternal Management and Risk

Maternal safety is the paramount consideration in fetal surgery. A series of 102 fetal operations in 94 monkeys permitted us to develop anesthetic, surgical, and tocolytic regimens for fetal surgery and demonstrate satisfactory maternal safety.[64–66]

Clinical Experience: Operative Technique

Perioperative clinical management principles are based directly on the experimental nonhuman primate work. Maternal preparation begins with a 100-mg suppository of indomethacin before operation and placement of an epidural catheter for postoperative analgesia. During operation halothane is used for uterine relaxation and for fetal and maternal anesthesia. After operation ritodrine, magnesium sulfate, and indomethacin are used for tocolysis. Maternal intraoperative monitoring includes a blood pressure cuff, large-bore intravenous catheters, a bladder catheter, electrocardiographic leads, and a transcutaneous pulse oximeter (Fig. 5).

The mother is positioned supine with towels placed under the right side to lift her uterus off of the inferior cava to avoid compromise of venous return. The uterus is exposed through a low transverse abdominal incision and delivered into the operative field. A large abdominal ring retractor is used to maintain exposure. Sterile intraoperative ultrasound is used to confirm the fetal position and placental location. The position and orientation of the hysterotomy is planned to stay as far away from the placenta as possible and still allow exposure of the appropriate part of the fetus. Excess amniotic fluid is aspirated with a trocar and kept warm. The hysterotomy can be performed with an absorbable stapler that is fast and hemostatic.[67] An alternative method to minimize blood loss during hysterotomy is by manual compression on either side of the proposed hysterotomy: the uterine incision then is made between the assistant's hands using electrocautery. Immediately thereafter specially designed compression clamps are placed around the edge of the uterine incision to prevent bleeding.

For urinary tract decompression,[25-27] the lower extremities of the fetus are exteriorized and a transcutaneous pulse oximeter is placed around the fetal thigh. A midline suprapubic incision is made through the fetal abdominal wall exposing the thick-walled and distended bladder. The bladder is then opened and marsupialized to the abdominal wall using interrupted 4-O silk sutures (Fig. 6).

For diaphragmatic hernia,[41,42] the left arm of the fetus is exteriorized for monitoring and the left side of the chest and upper abdomen is stabilized by placing a Babcock clamp onto the costal margin (Fig. 7). The diaphragm is repaired with a Gore-Tex patch through a subcostal incision and the abdomen is enlarged to accommodate the viscera using another synthetic patch (Fig. 8).

The fetus is returned to the uterine cavity and the amniotic fluid is restored with either warm normal saline or warm amniotic fluid containing 500 mg nafcillin. The uterus is closed with three layers of absorbable sutures and fibrin glue. The low transverse abdominal incision is closed in layers using running 0-PDS suture and the skin is closed with a subcuticular suture. Beyond these technical points, we have learned that, as a general principle, fetal surgery should be 'all or none,' *i.e.*, the fetal repair should be complete and adequate to ensure a good chance for fetal survival, or else the otherwise doomed fetus should be removed. A partial or inadequate repair presents an ongoing threat to the mother for little potential benefit.

Postoperative Management

Premature labor remains the largest obstacle to a successful outcome in the postoperative course. After operation uterine contractions and fetal heart rate are monitored and tocolytic therapy with betamimetics, magnesium sulfate, and prostaglandin synthetase inhibitors is adjusted accordingly. Once the initial period of uterine contractions has subsided (usually within 5 days), oral tocolytics gradually are substituted for intravenous drugs and then continued throughout the remainder of the pregnancy. Perioperative antibiotics, generally a cephalosporin, are continued for 3 days after operation. The patient is kept at bedrest for at least 3 days following surgery and then begins a progressive ambulation program. Postoperative adynamic ileus is common for 2 or 3 days, and oral intake resumes with the return of bowel function. Generally the patient is discharged on only oral tocolytic therapy within 10 days of the procedure.

Maternal Outcome

Between 1981 and 1989, 18 women have undergone open fetal surgery in the Fetal Treatment Program at

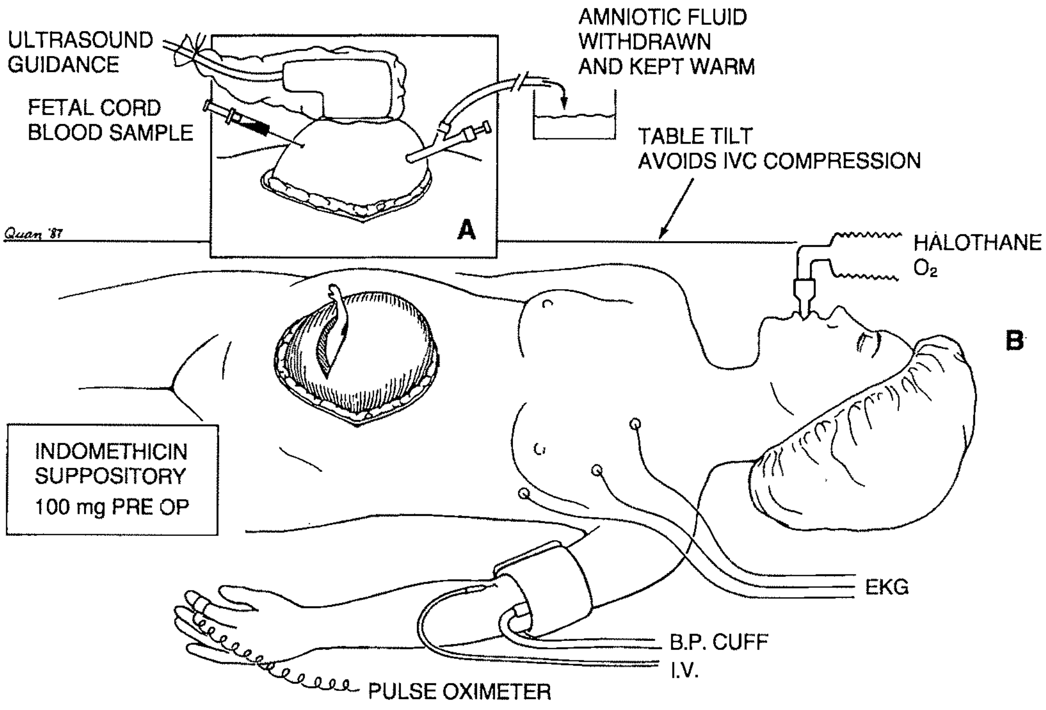

ULTRASOUND GUIDANCE
FETAL CORD BLOOD SAMPLE
AMNIOTIC FLUID WITHDRAWN AND KEPT WARM
TABLE TILT AVOIDS IVC COMPRESSION
A
Quan '87
HALOTHANE
O_2
B
INDOMETHICIN SUPPOSITORY 100 mg PRE OP
EKG
B.P. CUFF
I.V.
PULSE OXIMETER

FIG. 5. Drawing of maternal positioning and monitoring for open fetal surgery.

UCSF. The operations were performed for four indications: bladder outlet obstruction, congenital diaphragmatic hernia, sacrococcygeal teratoma, and congenital cystic adenomatoid malformation. Fifteen of the procedures were technically successful, resulting in a viable fetus after operation. In three cases the fetal anatomic problem proved to be irreparable at the time and the fetus was removed. Women with continuing pregnancies are committed to Cesarean section at the time of delivery.

Obviously maternal safety is the first priority in all cases. There have been no maternal deaths and few maternal complications. There was one case of mild antibiotic-associated pseudomembranous colitis that responded to oral vancomycin. One patient developed a small amniotic fluid leak from the hysterotomy site causing abdominal pain several weeks after she returned home. This was stopped easily during reoperation with a single suture and has not happened again since we changed our method of hysterotomy closure to three layers. The maternal mirror syndrome developed in two mothers after resection of fetal tumors as described above. This complication made control of preterm labor difficult and finally necessitated Cesarean delivery. Finally poor patient compliance occurred in one case—the mother stopped her oral tocolytics and promptly went into premature labor and delivered vaginally.

Effect on Reproductive Potential

One of the principal concerns following fetal surgery is the ability of the mother to carry further pregnancies. We first evaluated the potential for future reproduction after fetal surgery in a large series of nonhuman primates.[66] Computed medical records are maintained for each primate at the California Primate Research Center, Davis, California. This database provided reliable information regarding subsequent breeding and contraception and permitted comparison of our experimental fetal surgery group with the normal breeding colony. We found that in animals that had uterine closure with absorbable sutures, fetal surgery did not interfere with subsequent fertility.[62] However animals that had metal staple hysterotomy closure had a markedly decreased fertility rate. It is now clear that metal staples migrate through the uterine wall and we speculate that exposure of the endometrial cavity to permanent foreign body hinders fertility. Based on this experience, we no longer use the metal stapler for uterine closure and subsequently developed a stapler for hysterotomy that uses absorbable staples.[67]

Uterine rupture is a dreaded complication during labor following previous Cesarean section and it occurs more commonly after a classic Cesarean section than after a

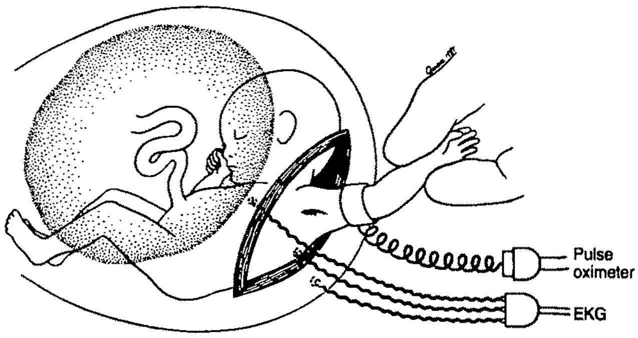


FIG. 7. Left arm and chest exteriorized and monitors placed with subcostal incision shown. A miniaturized radiotelemetry device can be placed subcutaneously for perioperative fetal EKG, temperature, and activity monitoring (reprinted with permission).

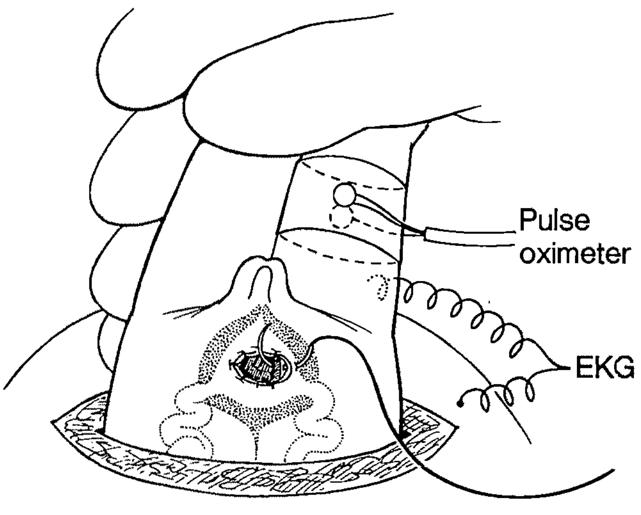


FIG. 6. Diagram of intraoperative appearance of bladder marsupialization to the fetal abdominal wall to create a vesicoamniotic fistula (reprinted with permission).

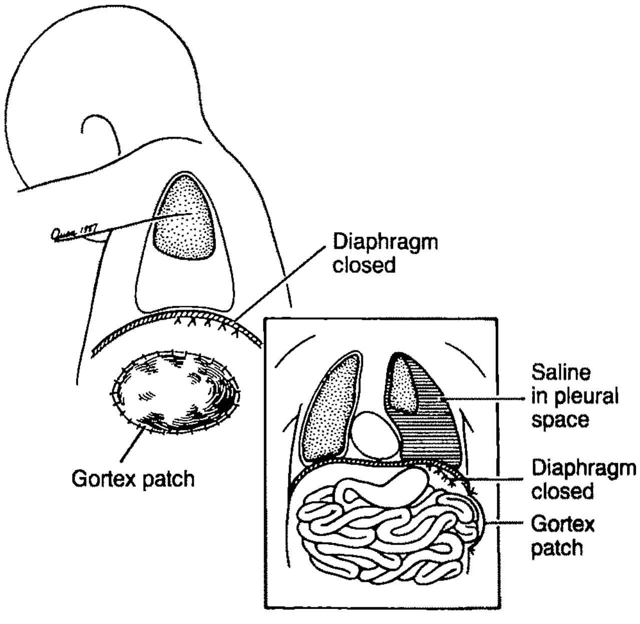


FIG. 8. Diaphragm closed. Abdomen enlarged with patch to accommodate viscera without increasing intra-abdominal pressure (reprinted with permission).

lower uterine segment incision. The hysterotomy used for fetal surgery is invariably in the upper segment of the uterine corpus and thus is comparable to a classic Cesarean section. In our nonhuman primate series there were five cases of uterine rupture, while 62 other primates labored and delivered vaginally without complication during the fetal surgery pregnancy. Based on this experience, Cesarean section delivery should be mandatory after fetal surgery to avoid rupture of the relatively fresh uterine wound.

In follow-up of our 18 patients, seven have had subsequent pregnancies, and all deliveries were by repeat Cesarean section with good outcome. The first patient has had two normal pregnancies. The remaining women are too close to their operative date to assess for fertility after fetal surgery.

From our experience in animals and in our initial clinical experience with open fetal surgery, we conclude that the anesthetic regimen first developed in the nonhuman primate model has been used successfully in humans, with an acceptable perioperative risk. The paucity of complications in the first 18 patients with open fetal procedures is a direct result of our extensive preparation in experimental fetal animals, which should be a prerequisite for anyone contemplating these procedures. We know of only one other human open fetal surgical case that was performed at a medical center where the investigators chose not to do preparatory work in nonhuman primates, and that procedure failed.

The uterine irritability induced by hysterotomy can be suppressed successfully during operation with halothane anesthesia and after operation with intravenous and oral tocolytic agents, but premature labor remains a serious and frequent problem with fetal surgery, requiring early confinement in most cases. The morbidity associated with management of preterm labor will be reduced with further experience. Finally the clinical and experimental evidence suggests that a mid-gestation hysterotomy, closed with absorbable sutures, does not adversely effect future fertility.

Our ability to diagnose fetal birth defects has achieved considerable sophistication and offers new hope for improved management of the fetus with a life-threatening defect. However the more invasive diagnostic and therapeutic procedures involve significant risks for both fetus and mother, raising difficult ethical questions about risks compared to benefits and about the rights of the fetus and the mother. It is imperative that all who consider embarking on this type of treatment be committed to developing continuously the enterprise through ongoing research and responsible reporting of all clinical experience. With continuing research and cautious clinical experience, the indications for fetal therapy undoubtedly will continue to expand.

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Studies in Fetal Wound Healing

V. A Prolonged Presence of Hyaluronic Acid Characterizes Fetal Wound Fluid

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Midgestation fetal wound healing is characterized by healing without fibrosis or scar formation. The mechanisms that underlie this remarkable process are mediated in part through a fetal wound extracellular matrix rich in hyaluronic acid. In this study a newly developed assay was used to determine the hyaluronic acid levels in fetal and adult wound fluid. Adult wound fluid had a rapid increase in hyaluronic acid, which peaked at 3 days and decreased to 0 by 7 days. In contrast levels of hyaluronic acid in fetal wound fluid increased rapidly and remained significantly elevated for 3 weeks. This prolonged presence of hyaluronic acid in the matrix of fetal wounds creates a 'permissive' wound environment that promotes fetal fibroblast movement and proliferation and inhibits cytodifferentiation. Such a matrix environment promotes healing by regeneration rather than by scarring. This observation has therapeutic implications. The prolonged application of hyaluronic acid or hyaluronate protein complexes to wounds in children or adults may modulate healing in a manner that makes the wounds more fetal-like.

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ADULT WOUND REPAIR is characterized by fibrosis, scarring, and sometimes by contracture. The results of this deforming process affect every form of surgery and can have devastating consequences. In contrast fetal wound healing proceeds without such fibrosis or scar formation.[1-19] Previously we showed that a transition from fetal- to adult-type repair occurs midway through the last trimester.[11] The observations from our initial clinical series of fetal surgery at the University of California at San Francisco (UCSF) support these experimental findings.[20,21]

Although the mechanisms that endow fetal wound healing with these unique qualities remain enigmatic, this process is mediated in part through the extracellular matrix (ECM). DePalma and coworkers[8,14] demonstrated that the fetal wound ECM is rich in hyaluronic acid (HA), a glycosaminoglycan found in high concentrations whenever rapid cell movement and proliferation occur.[22,23] The deposition of HA and its subsequent degradation by the enzyme hyaluronidase play critical roles in a number of experimental model systems during early embryogenesis.[23] Hyaluronic acid also was found to enhance postnatal wound healing and reduce adhesions after tendon repair.[24-26] Therefore we postulate that a wound ECM rich in HA provides a permissive environment for repair, free of scar formation, and that HA is one of the ECM components that endow fetal wound healing with its unique properties.

Previously we demonstrated a mechanism for HA deposition in fetal wounds; an elevated HA-stimulating activity (HASA) has been identified in fetal wound fluid.[19] The HASA remained elevated from 1 to 14 days in fetal wound fluid, whereas it was not detected at any time in adult wound fluid samples. This observation, together with that of DePalma et al.,[8,14] led us to postulate that there may be a prolonged presence of HA in the fetal wound ECM. Herein, using a wire-mesh cylinder model, we demonstrate that fetal wound fluid indeed has a prolonged presence of HA, from 1 to 21 days after wounding. In contrast HA was present only initially in adult wound fluid. Thus the prolonged presence of HA is unique to fetal wound fluid and may provide a component of the ECM environment that underlies a process of wound repair that occurs without fibrosis or scarring.

Materials and Methods

Wound Cylinders

Sterile wire mesh cylinders were used as described by Schilling and Hunt.[27,28] The cylinders were prepared by

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cutting a rectangle from No.40 mesh, 36-gauge stainless steel. Cylinders were rolled into a tube and the ends folded closed. Fetal cylinders measured 1 × 3 cm and the adult cylinders measured 3 × 6 cm.

Animals

Seven time-dated, pregnant ewes from Torrel Farms (Ukiah, CA) were transferred to the UCSF animal care facility and fed food and water *ad libidum*. The animals were fasted for 48 hours before surgery.

Fetal Wound Fluid

At 100 days' gestation (145 days = term), the animals underwent general halothane/oxygen anesthesia using techniques developed specifically for fetal lamb surgery as previously described.[29] Ewes were immobilized by 1000 mg of Ketamine (Vetalar®; Parke-Davis, Morris Plains, NJ) and underwent induction of general halothane/oxygen anesthesia by mask, followed by placement of a #10 oral endotracheal tube. A 16-gauge intravenous catheter (Deseret, Sandy, UT) was inserted percutaneously into the single jugular vein and 500 mL of Lactated Ringer's solution (Baxter Health Care Corp., Deerfield, IL) containing 4 × 10^6 units of penicillin G (Pfizer, New York, NY) and 400 mg of Kanamycin (Kantrim®; Bristol-Meyers, Syracuse, NY) was infused during the procedure. The maternal abdomen was prepped and draped using sterile techniques and a midline laparotomy was performed. Using a GIA (U.S. Surgical, Norwalk, CT) stapler, the fetal lamb was exposed by hysterotomy. The fetal position was manipulated to expose only one limb at a time and a warm moist towel was wrapped around the uterus to help keep the fetus warm. Two-centimeter incisions were made in both the groin and axillary creases at sites where excess skin folds were observed. A small, subcutaneous pocket was created by blunt dissection and a single wound cylinder was placed in each pocket. The wounds were closed in one layer using interrupted 4–0 silk sutures (Ethicon, Somerville, NJ). The fetus was returned to the uterus and amniotic fluid volume was restored with sterile saline. The hysterotomy was closed, including the membranes, with a TA-90 (U.S. Surgical) stapler. The laparotomy was closed in layers and the ewe was returned to her stall.

Subcutaneous wound cylinders were placed in seven fetal lambs. A separate lamb was used for each time point of fluid harvest. At the designated time of harvest (1, 2, 3, 7, 10, 14, or 21 days after implantation), the maternal ewe underwent general anesthesia as described above. Following laparotomy and hysterotomy, the fetus was exposed. Fetal wound fluid was harvested from wound cylinders (four cylinders per animal) by a single percutaneous aspiration under sterile technique during reoperation using an #18-gauge needle and a 12-mL syringe. The fluid was frozen immediately and stored at −70°C until analysis.

Adult Wound Fluid

Maternal ewes were used for the adult data points. At the conclusion of the fetal procedure, four large wound cylinders were placed in widely separated subcutaneous pockets along the maternal flank. Wounds were closed with interrupted 2–0 silk sutures (Ethicon). Adult wound fluid was harvested at the same time points as fetal fluid by aspirating the wound cylinders, again using sterile techniques. The fluid was frozen immediately and stored at −70°C until analysis.

[^{35}S] Streptavidin Hyaluronic Acid-binding Protein Assay

Following thawing, all samples were passed through a 22-μm filter (CoStar, Cambridge, MA) and assayed using a newly developed [^{35}S] streptavidin HA-binding protein (HABP) assay modified from Tenglbad.[30] Briefly, 100-μl samples of equilibrated digests were aliquoted into the upper chambers of CoStar Spin-X filter units (CoStar, Cambridge, MA). Aliqouts (150 μl) of HABP diluted 1:50 in assay buffer were then added. The solutions were mixed and rotated on an American Rotator V (American Scientific, McGaw Park, IL) at 160 rpm for 30 minutes at room temperature to allow the HA in the tissue extract to bind to HABP. Next 60 μl of HA gel diluted 1:15 as above was added. The solutions were mixed and then rotated as above for 60 minutes to allow the free HABP to bind to the gel. Samples were spun at 11,000*g* for 5 minutes and the filtrate then passed into the filter units' lower chamber. The HA gel was resuspended in 200 μl assay buffer as a wash and spun for 5 minutes as above. Next 200 μl of [^{35}S] streptavidin (1000 Ci/mmole, 100 μCI/mL; Amersham, Arlington Heights, IL) diluted 1:200 in phosphate-buffered saline–calcium magnesium free (PBS-CMF) were added, the pellet was resuspended and rotated for 30 minutes, and spun for 5 minutes as above. As a final wash the pellet was resuspended in 200 μl of PBS-CMF and spun as above. The HA-gel pellet was transferred to counting vials with distilled water and Optifluor® scintillation fluid (Packard, Downers Grove, IL) was added. Nonspecific streptavidin binding was determined by assaying samples without HABP. This was subtracted from all values. A standard curve was constructed using known concentrations of HA and expressed as a percentage of control value. Values from control samples without added HA were considered to be 100% bound. All samples were assayed in triplicate. The data for each sample, run in triplicate, were expressed as the mean value ± standard deviation.

Results

All seven ewes and fetuses survived the experimental protocol. No animal developed infection.

Adult Wound Fluid

Wound fluid from the seven maternal ewes was aspirated sterilely and assayed for HA levels. The volume of wound fluid aspirated per cylinder tended to increase from an average of 1 to 2 mL at 1 day to 4 to 5 mL at 21 days. Previous attempts to harvest wound fluid earlier than 1 day yielded less than 1 mL. The HA levels increased sharply during the first 3 days, reaching a peak level of 7.0 ± 1.2 μg at day 3. By 7 days the HA level had decreased to 0.0 ± 0.9 μg and remained undetectable thereafter to 21 days, the last time point to be determined (Fig. 1).

Fetal Wound Fluid

Fetal wound fluid also was obtained by sterile needle aspiration and assayed for HA levels. The volume of wound fluid aspirated per cylinder tended to increase from an average of 1.5 to 2 mL at 1 day to 3 to 4 mL at 21 days. As with adult cylinders, previous attempts to harvest wound fluid earlier than 1 day yielded less than 1 mL. The level of HA increased in a pattern similar to adult wound fluid during the first 3 days, reaching a peak of 4.6 ± 1.4 μg at day 3 (Fig. 1). In contrast to the adult, HA levels remained elevated throughout the 21 days. The differences between fetal and adult HA levels were statistically significant at $p < 0.01$ for the 10-, 14-, and 21-day data points using the Student's t test.

Discussion

The ECM of fetal wounds is rich in glycosaminoglycans, particularly HA.[8,14] Hyaluronic acid is a large molecule that plays a prominent role in the structure of the ECM and is found whenever rapid cell proliferation, motility, and dedifferentiation occur. This molecule also suppresses differentiation.[22] We postulated that HA is deposited early in the course of both fetal and adult wound healing, but its deposition is sustained throughout the course of fetal wound healing. Thus a matrix with a prolonged presence of HA is a characteristic of fetal wound healing.

The purpose of this study was to examine this hypothesis by analyzing fetal and adult wounds for their level of HA. We used the Schilling–Hunt wire-mesh cylinder model[27,28] to sample wound fluid from 1 to 21 days after implantation. We previously showed that incisional wounds in 100-day gestation fetal lambs (the same gestational age that the cylinders were implanted in this study) healed without scar formation during the 14 days of observation.[11] By harvesting fluid at intervals from 1 to 21 days, we sampled a full spectrum of fetal wound healing, from early to late.

Fetal wound cylinder implantation sites of the groin and axilla were chosen because the excess skin folds and subcutaneous space in these locations most easily accepted the fetal cylinder from a technical standpoint. Flank implantation sites in the adult ewe were chosen from ex-

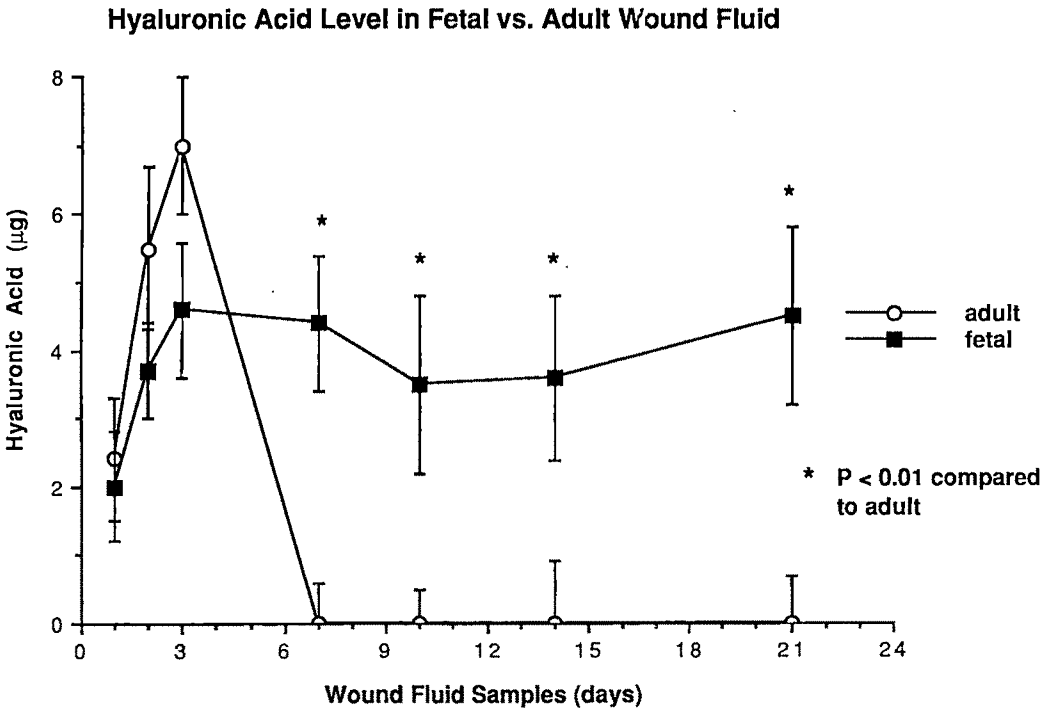

FIG. 1. HA levels in adult and fetal wound fluid. As detailed in Materials and Methods, 100 μL of wound fluid at each time point was assayed using a newly developed HABP assay. Error bars represent the standard deviation of each value run in triplicate. Student's *t* test was used for statistical analysis.

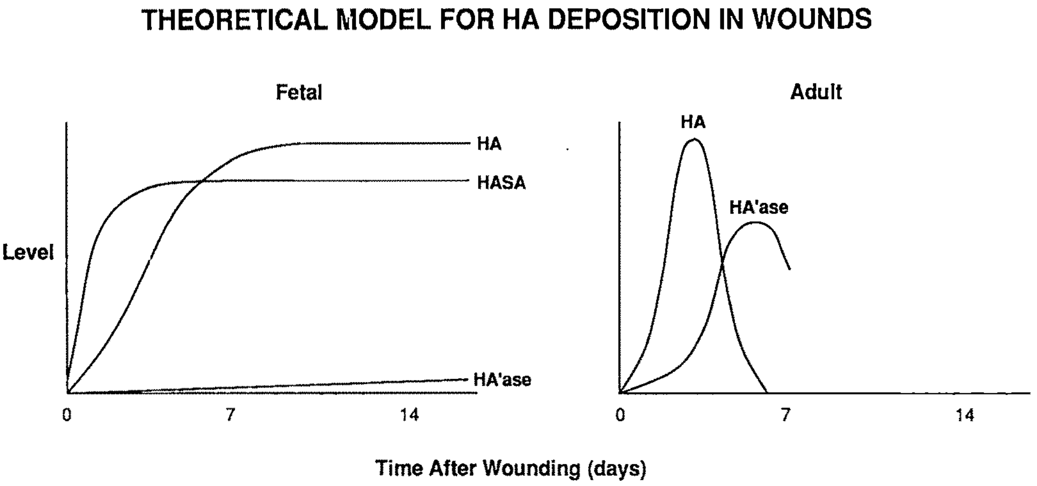

FIG. 2. Conceptualized drawing for the mechanism of HA deposition in wounds. In fetal wounds, HASA increases before HA and the sustained elevation of HASA underlies the prolonged presence of HA. In contrast HASA is not present in adult wounds at any time. HA is present only initially and is subsequently degraded by hyaluronidase.

perience and convenience. Adult sheep spend a great deal of time in the prone position and crush wound cylinders implanted in the groins, axilla, or abdomen. The wound cylinder must maintain its shape to create dead space and the flattened cylinders failed to yield wound fluid. The subcutaneous space over the rib cage is not well developed and it is technically difficult to implant the large adult cylinder into it. Finally implanting wound cylinders into the flanks of ewes was technically easy and allowed us to avoid the problems associated with the other potential sites.

The fetal and adult data differed dramatically. Hyaluronic acid was present early in both fetal and adult fluid. However after 3 days HA essentially was undetectable in the adult samples, whereas it remained significantly elevated in fetal samples between 7 and 21 days.

We recently documented a mechanism for the modulation of HA deposition in the fetus. Fetal serum, amniotic fluid, wound fluid, and a number of fetal tissues all contain HASA.[15,16,19,31,32] Fetal wound fluid contained increased HASA levels in samples harvested from 1 to 14 days after wounding.[19] The prolonged elevation of HASA is one likely mechanism for the persistent presence of HA in fetal wound fluid. Based on these studies we developed a conceptualized model for prolonged HA deposition in fetal wounds (Fig. 2). Our model suggests that hyaluronidase activity increases in the adult wound after 3 days. Studies are in progress to evaluate the activity of hyaluronidase and its inhibitors in fetal and adult wound fluid.

The prolonged presence of HA in fetal wounds provides a unique environment that promotes the highly ordered matrix observed in the ECM of fetal wounds. We previously showed that collagen is deposited rapidly and in a pattern indistinguishable from unwounded fetal skin in 100-day gestation lambs.[11] The signals for this type of organization may be mediated through a wound matrix rich in HA. Hyaluronic acid is known to affect collagen synthesis. Chandrakasan et al.[33] demonstrated that the deposition of type III collagen by fibroblasts is elevated by exogenous HA added to the media. Normal fetal tissue and granulation tissue have a much higher content of type III collagen that does normal adult tissue.[34] Scott and Hughes[35] noted that early in development, fetal collagen fibrils were smaller in diameter when HA was more abundant. Furthermore the ratio of type I to type III collagen determines the diameter of collagen fibrils.[36,37] These studies provide convincing evidence that collagen organization in the process of fetal wound healing is modulated by the presence of HA in the ECM.

Our previous work demonstrated a 'spectrum' of fetal incisional wound healing patterns, with a transition to adult-type healing and scar formation midway through the last trimester in fetal lambs.[11] Wound fluid from cylinders implanted late in gestation (*i.e.*, at 120 days) may show an adultlike pattern of HA deposition. If this is true, the pattern of HA in wound fluid can be used as a marker for 'fetal' or 'adult' phenotype in wound repair. Studies are underway to investigate this possibility.

The finding of a prolonged presence of HA in fetal wound fluid and its association with scar-free healing has major clinical implications. Hyaluronic acid has been demonstrated to enhance postnatal healing following tympanic membrane perforation and scratch incision.[24,25] Hyaluronic acid also was shown to decrease adhesions after tendon repair.[26] Thus it may be possible to modulate wound healing in children and adults to become more fetal-like, by the prolonged application of HA or HA-protein complexes to the healing wound.[38]

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Have Changing Treatment Patterns Affected Outcome for Operable Breast Cancer?

Ten-year Follow-up in 1288 Patients, 1965 to 1978

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From 1965 to 1978, 1288 patients with primary operable breast cancer were treated by the senior author, using extended radical (ERM), radical (RM), and modified radical (MRM) mastectomy operations exclusively. Results were analyzed for trends in overall and disease-free survival, and patterns of local and distant relapse, the years 1965 to 1970 *versus* 1971 to 1974 *versus* 1975 to 1978. Significant changes ($p < 0.00001$) from 1965 to 1978 included progressively earlier stage of disease, less frequent use of RM and ERM, a decline in the use of postoperative radiotherapy, and the introduction in 1975 of multidrug adjuvant chemotherapy. Ten-year disease-free survival rates improved significantly for all patients (by 11%, $p = 0.00004$) and for node-negative (by 12%, $p = 0.0024$), node-positive (by 8%, $p = 0.012$), clinical stage II (by 15%, $p = 0.0022$), and pathologic stage II (by 12%, $p = 0.016$) disease. Ten-year local recurrence for all patients was 3% (local only) and 2% (local with distant metastasis), and survival from date of recurrence for all patients failing treatment increased two times ($p < 0.0001$) for patients treated most recently. As the primary surgical treatment of breast cancer continues to become more moderate, the promise of systemic adjuvant therapies can be realized only with continued emphasis on earlier diagnosis and maximal local control of disease.

IN THE LAST TWO decades we have witnessed remarkable changes in the management of primary operable breast carcinoma. The Halstead radical mastectomy, a standard since the 1890s, has yielded to modified radical mastectomy and breast-conserving approaches combining surgery and radiotherapy, encouraged by the results of randomized trials with follow-up now exceeding 10 years.[1,2] Postmastectomy radiotherapy has been used with decreasing frequency, particularly for stages I and II disease, and systemic adjuvant therapy (cytotoxic and hormonal) has come into widespread use. Despite these factors nationwide survival statistics for operable breast cancer have not improved significantly in recent decades[3] and no long-term studies have demonstrated survival rates for breast conservation exceeding those of comparable patients treated by radical surgery. This study reports the results of a large single-surgeon experience with 1288 patients treated from 1965 to 1978 and followed 10 years, with particular attention to trends in pattern of primary treatment, local/distant failure, and long-term survival. Because the primary treatment of breast cancer has become increasingly heterogeneous in the 1980s, these patients (treated exclusively by radical surgery) comprise a unique historical reference for future studies.

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Patients and Methods

Between 1965 and 1978, 1395 patients with primary operable breast carcinoma were treated by the senior author (J.A. Urban) on the Breast Service, Department of Surgery, at Memorial Sloan-Kettering Cancer Center. Excluding 107 patients with noninvasive tumors (intraductal or lobular carcinoma *in situ*), 1288 patients with invasive carcinomas form the basis of this study and were grouped into three cohorts: 1965 to 1970 (493 patients), 1971 to 1974 (347 patients), and 1975 to 1978 (448 patients). The 1965 to 1970 patients formed the basis of a previous report,[4] but for this study all data were updated and reanalyzed with particular attention to patterns of local recurrence.

All patients were judged to have operable disease and the only criteria of inoperability were supraclavicular dis-

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ease, arm edema, inflammatory carcinoma, distant metastases, or medical contraindications to general anesthesia. Excluded were patients with a previous breast (or other) cancer, but patients with bilateral (synchronous or subsequent) breast cancers were included.

All were treated by radical surgery, using radical mastectomy (RM), extended radical mastectomy (ERM), and modified radical mastectomy (MRM) selectively. Modified radical mastectomy was used for patients with the smallest tumors and clinically negative axillae. Extended radical mastectomy was used for patients with larger, medially located tumors and RM for the remaining patients. Operative technique was as previously described.[5] All patients had full axillary dissections and no special nodal 'clearing' methods were used in pathologic examination. Contralateral breast biopsy was performed in most cases.

TABLE 1. *Patient and Tumor Characteristics*

Data	1965–1970	1971–1974	1975–1978
No. patients	493	347	448
Age: Mean (years)	54.5	55.8	56
Range	22–85	26–85	25–87
% <50	37	29	30
Tumor location			
UOQ%	41	44	47
LOQ%	22	14	11
UIQ%	21	22	22
LIQ%	7	10	9
C%	9	7	9
Tumor size (cm)			
Clinical			
Mean	NA	2.7	2.3
Median	NA	2.0	2.0
Range	NA	0.5–9.0	0.3–8.0
Pathologic			
Mean	2.5	2.4	2.2
Median	2.0	2.0	2.0
Range	0.2–9.8	0.3–9.0	0.3–9.0
Tumor type			
Inv. duct%	92	95	94
Inv. lobular%	8	5	6
Favorable % (incl. medullary, colloid, tubular, papillary)	3	4	3
Axillary nodes			
Clinical			
Neg. (N0, N1a)%	75	84	83
Pos. (N1b)%	25	16	17
Pathologic			
nodes removed (mean #)			
Ax, level I	NA	11	13
Ax. level II	NA	6	5
Ax. level III	NA	6	5
Total	NA	23	23
Highest level positive			
Neg. %	56	61	59
I%	22	22	24
II%	11	8	9
III%	11	9	8
No. nodes positive			
0%	56	61	59
1–3%	44	28	25
>3%		11	16
Micromets			
Only %	NA	8	9

UOQ, upper outer quadrant; LOQ, lower outer quadrant; UIQ, upper inner quadrant; LIQ, lower inner quadrant; C, central; NA, not applicable.

TABLE 2A. *Patterns of Treatment by Years Treated*

Treatment	1965–1970	1971–1974	1975–1978
Operation			
RM # (%)	351 (71)	227 (65)	193 (43)
ERM # (%)	102 (21)	48 (14)	45 (10)
MRM # (%)	40 (8)	72 (21)	210 (47)
Contralat BX			
Pos. %	7.3	10.4	10.7
Neg. %	75	76.3	80
Not done %	17.7	13.3	9.3
Postop RT			
Yes %	42	33	27
No %	58	67	73
Chemotherapy			
Yes %*	0	0	19
No %	100	100	81

All patients were staged clinically and pathologically using the 1983 American Joint Committee on Cancer classification (stage I, T1N0; stage II, T2N0, T1-2N1; stage III, T3N0-1).[6] Follow-up for most patients was maintained by regular in-office examination, and for the remaining patients from hospital records, by telephone, and by questionnaire; median follow-up was 10.3 years and was complete at 5 years in 97% and at 10 years in 93% of all patients.

Statistical Methods

All statistical analyses were done using BMDP programs (BMDP Statistical Software, Los Angeles, CA, 1988 re-

TABLE 2B. *Operation Type by Stage of Disease*

Operation	I	II	III	Total
		Clinical Stage # (%)		
RM	342 (51)	373 (70)	46 (65)	761 (60)
ERM	78 (11)	102 (19)	15 (20)	195 (15)
MRM	253 (38)	57 (11)	22 (15)	322 (25)
Total	673 (100)	532 (100)	83 (100)	1288 (100)
		Pathologic Stage # (%)		
RM	242 (49)	474 (67)	45 (70)	761 (60)
ERM	55 (11)	125 (18)	15 (21)	195 (15)
MRM	207 (40)	117 (15)	8 (9)	322 (25)
Total	504 (100)	716 (100)	68 (100)	1288 (100)

RM, radical mastectomy; ERM, extended radical mastectomy; MRM, modified radical mastectomy.

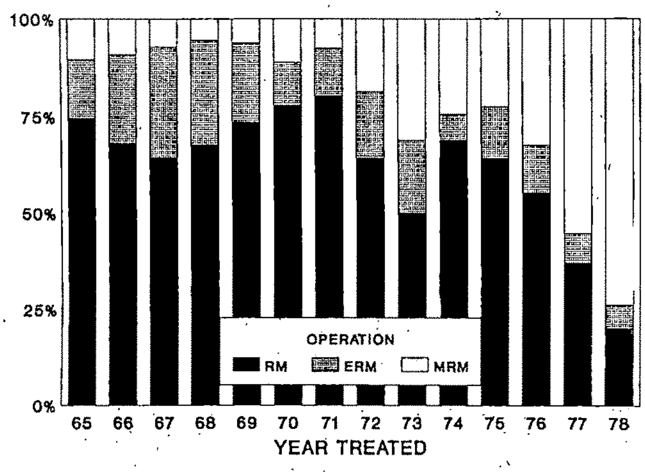


FIG. 1. Distribution of operation type by year of treatment, 1965–1978 ($p < 0.00001$).

lease) on an IBM PS/2 Model 70 E61 computer (IBM, Armouk, NY). Overall and disease-free survival rates were determined using the life table method (BMDP 1L). Patients dying of other causes and known to be cancer free were censored, while patients dying of unknown causes were considered dead of disease. The significance of survival differences was tested by the log rank method (BMDP 1L), univariate comparison of group means by Student's t test (BMDP 3D), and association between categorical variables by the Pearson chi square test (BMDP 4F). Multivariate analysis employed the Cox proportional hazards model, using stepwise regression by the maximized partial likelihood ratio method (BMDP 2L).[7]

Results

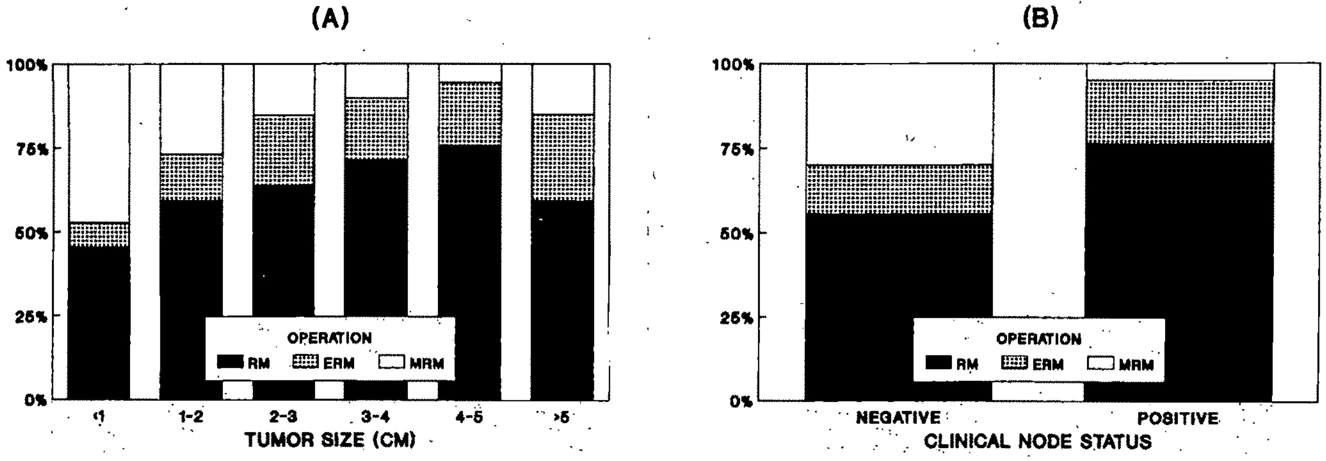
Table 1 compares a variety of patient and tumor characteristics among the three time cohorts. Although median tumor size was constant), there was a significant trend toward smaller mean size ($p = 0.0001$).

Fewer patients in more recent years had clinically positive axillae ($p = 0.003$), although the pathologic extent of axillary node involvement by highest level of metastasis did not change significantly from 1965 to 1978 ($p = 0.35$). Before 1971 axillary involvement was only described by anatomic level and not by number of nodes involved; from 1971 and after, exact numbers of nodes removed and involved were noted for most patients and did not change significantly from 1971 to 1978 ($p = 0.35$).

All patients were treated by radical surgery (Table 2A), with a significant trend during the period studied toward fewer RM and ERM, and more MRM (Fig. 1, $p < 0.0001$). Extent of surgery was based both on tumor size and on clinical axillary node status (Fig. 2, $p < 0.00001$). Operation type was significantly correlated with clinical and pathologic stage of disease (Table 2B, $p < 0.00005$).

Postoperative radiotherapy was used less often in recent years ($p < 0.0001$). Multidrug adjuvant chemotherapy was used only since 1975; in this study patients given chemotherapy for less than 6 months or who were given single-dose or single-drug regimens were considered not to have been treated. About one third of patients with one to three nodes positive and two thirds with more than three nodes positive received chemotherapy since 1975 (Table 3). Four node-negative patients thought to be at high risk based on tumor size and/or extensive lymphatic permeation also received chemotherapy.

All patients were staged both clinically and pathologically (Table 4). More patients in recent years had stage I disease, both clinical ($p = 0.001$) and pathologic ($p = 0.005$). This downstaging appears to be a result of progressively smaller tumor sizes and fewer patients with



FIGS. 2A and B. Selection of operation type by (A) tumor size ($p < 0.00001$) and (B) clinical node status ($p < 0.00001$).

TABLE 3. *Patterns of Chemotherapy Use, 1975–1978*

		% Receiving Chemotherapy	
Nodal Status	Premenopause	Postmenopause	Total
Node negative	2.6	1.1	1.5
1–3 Nodes	33	28	30
>3 Nodes	64	64	64
Total	20	18	19

clinically positive axillae, although as noted above, pathologic extent (by level or number) of axillary nodal disease did not change significantly during this period.

Tables 5 and 6 list 5 and 10-year overall and disease-free survival rates for the entire patient group, by nodal and menopausal status, clinical and pathologic stage, and pathologic TNM status. Of note are the 10-year disease-free survival rates for node-positive disease: 55% for all node-positive, 48% for pathologic stage III, and 34% for patients with level III axillary node involvement.

In Tables 7 to 10, survival by stage, menopausal and nodal status is listed, comparing the results within each subgrouping by chronologic cohorts. Table 7 demonstrates survival improvement in the period studied for all patients, node negatives, and node positives, all with significant probability values.

Survival by menopausal status and number of axillary metastases (Table 10) is reported only for 1971 to 1974 and 1975 to 1978; exact numbers of nodes were not reported before 1971. The most striking, and only significant, improvement is seen in the premenopausal, one to three node-positive group, although small numbers of patients are involved, and only one third of the 1975 to 1978 group received adjuvant chemotherapy (Table 3). No significant improvement was noted in any other grouping by menopausal status and number of axillary metastases.

Tables 11 and 12 list patterns of 10-year local recurrence, for all patients whose first site of treatment failure was a local recurrence (parasternal, skin flap, chest wall, or axillary) without evidence of distant metastases. Supraclavicular node relapse was not considered a local failure. An additional 2% of the entire group had local recurrence coincident with (or subsequent to) the development of distant metastases. By clinical and pathologic stage (Table 12), local recurrence increased with increasing stage. Because of the small numbers of patients developing local recurrence, there were no significant differences in

TABLE 4. *Stage of Disease*

Stage	1965–1970	1971–1974	1975–1978
AJC Clinical			
I # (%)	225 (46)	178 (51)	270 (60)
II # (%)	245 (49)	139 (40)	148 (33)
III # (%)	23 (5)	30 (9)	30 (7)
AJC Pathologic			
I # (%)	165 (34)	138 (40)	201 (44)
II # (%)	305 (62)	188 (54)	223 (50)
III # (%)	23 (4)	21 (6)	24 (6)

TABLE 5. *Survival Totals by Nodal Status, 1965–1978*

		5 Years		10 Years	
Nodal Status	No. Patients	Overall %	NED %	Overall %	NED %
Premenopause					
Node neg.	230	95	88	90	85
Node pos.	186	76	63	65	57
Total	416	87	77	79	72
Postmenopause					
Node neg.	521	92	87	88	80
Node pos.	351	79	65	63	54
Total	872	87	78	78	70
All Patients					
Node neg.	750	93	87	89	82
Node pos.	538	78	65	64	55
L I +	299	85	74	71	64
L II +	117	81	64	67	55
L III +	122	60	43	43	34
Total	1288	87	78	79	71

NED, no evidence of disease.

TABLE 6. *Survival Totals by Stage and TNM Status, 1965–1978*

		5 Years		10 Years	
Stage	No. Patients	Overall %	NED %	Overall %	NED %
		Clinical			
I	673	94	87	88	81
II	532	80	69	68	60
III	83	72	61	69	55
		Pathologic			
I	504	96	91	93	87
II	716	82	70	69	61
III	68	67	54	61	48
		TNM (Pathologic)			
T1N0	504	96	91	93	87
T2N0	237	86	78	79	73
T3N0	23	100	94	100	83
T1N1	215	86	74	76	67
T2N1	264	74	58	54	45
T3N1	45	61	52	53	48
Total	1288	87	78	79	71

NED, no evidence of disease.

TABLE 7. *Survival by Nodal Status*

		5 Years		10 Years	
Nodal Status	No. Patients	Overall %	NED %	Overall %	NED %
Node Negative					
1965–1970	274	88	82	82	75
1971–1974	213	95	90	89	84
1975–1978	263	97	91	96	87
					(p = 0.0024)
Node Positive					
1965–1970	219	71	62	58	51
1971–1974	134	74	61	58	56
1975–1978	185	92	70	77	59
					(p = 0.012)
Total Patients					
1965–1970	493	81	73	72	65
1971–1974	347	87	79	77	73
1975–1978	448	95	82	89	76
					(p = 0.0004)

NED, no evidence of disease.

TABLE 8. *Survival by Year Treated*

		5 Years		10 Years	
Stage/Years	No. Patients	Overall %	NED %	Overall %	NED %
		Clinical Stage			
Stage I					
1965–1970	225	91	86	86	79
1971–1974	178	94	88	88	83
1975–1978	270	97	88	91	82
					(p = 0.72)
Stage II					
1965–1970	245	72	63	58	52
1971–1974	139	82	72	70	67
1975–1978	148	93	76	85	67
					(p = 0.0022)
Stage III					
1965–1970	23	64	56	64	50
1971–1974	30	63	53	52	45
1975–1978	30	85	67	80	62
					(p = 0.39)
		Pathologic Stage			
Stage I					
1965–1970	165	93	88	88	83
1971–1974	138	98	93	94	89
1975–1978	201	98	93	97	89
					(p = 0.22)
Stage II					
1965–1970	305	75	66	62	55
1971–1974	188	82	71	68	65
1975–1978	223	93	75	81	67
					(p = 0.016)
Stage III					
1965–1970	23	64	56	64	50
1971–1974	21	56	47	45	41
1975–1978	24	80	59	73	53
					(p = 0.69)

NED, no evidence of disease.

TABLE 9. *Survival by Menopausal and Nodal Status*

		5 Years		10 Years	
Years	No. Patients	Overall %	NED %	Overall %	NED %
Premenopausal					
		Node Negative			
1965–1970	99	91	86	86	82
1971–1974	51	96	90	87	87
1975–1978	80	98	90	98	85
					(p = 0.76)
		Node Positive			
1965–1970	85	68	60	59	51
1971–1974	49	75	59	58	54
1975–1978	52	93	73	82	69
					(p = 0.13)
		Total			
1965–1970	184	80	74	74	68
1971–1974	100	86	75	73	71
1975–1978	132	97	83	93	79
					(p = 0.07)
Postmenopausal					
		Node Negative			
1965–1970	175	87	80	79	71
1971–1974	162	94	89	90	83
1975–1978	184	96	91	94	89
					(p = 0.00[illegible]6)
		Node Positive			
1965–1970	134	73	63	57	50
1971–1974	85	73	62	58	57
1975–1978	132	91	69	75	55
					(p = 0.52
		Total			
1965–1970	309	81	73	70	62
1971–1974	248	87	80	79	74
1975–1978	316	94	82	87	75
					(p = 0.0[illegible]18)

NED, no evidence of disease.

local recurrence rates by year of treatment in either the entire patient group (p = 0.13) or in any subgrouping by stage or extent of axillary involvement.

Table 13 reports 5-year survival from date of first treatment failure for all patients who experienced recurrence, by site of first recurrence, local-only *versus* local-with-distant, and distant-only. These survival rates improve strikingly for the most recent patient group (1975 to 1978), and by a significant margin in the larger group with distant disease. Expressed as months of median survival (± SEM),

TABLE 10. *Survival by Menopausal Status and Number of Nodes Positive*

		5 Years		10 Years	
Years	No. Patients	Overall %	NED %	Overall %	NED %
Premenopausal					
		1–3 Nodes+			
1971–1974	40	73	57	53	51
1975–1978	32	97	87	87	83
					(p = 0.01)
Total	72	83	70	67	65
		>3 Nodes+			
1971–1974	9	75	50	63	50
1975–1978	20	88	56	74	50
					(p = 0.61)
Total	29	84	54	70	50
Postmenopausal					
		1–3 Nodes+			
1971–1974	58	78	73	65	65
1975–1978	81	91	76	80	66
					(p = 0.96)
Total	139	86	75	73	66
		>3 Nodes+			
1971–1974	27	61	37	37	33
1975–1978	52	91	58	68	38
					(p = 0.18)
Total	79	79	50	56	36
		Total Patients			
		1–3 Nodes +			
1971–1978	211	85	73	71	66
		>3 Nodes +			
1971–1978	108	81	52	60	40

NED, no evidence of disease.

a similar improvement was seen for all patients failing treatment: 22 (± 3) for patients from 1965 to 1974 *versus* 55 (± 15) for patients from 1975 to 1978. Of note in these survival-from-date-of-recurrence statistics is the rapid occurrence of censoring in all groups of patients (most have distant metastases), which may distort the accuracy of statistical comparisons between groups, *i.e.*, if all censoring in the 1975 to 1978 cohort occurred as a result of death from disease, then, in fact, the observed survival advantage may only be an artifact.

TABLE 11. *Local Recurrence by Nodal Status*

Nodal Status	No. Patients	Local Recurrence %
Node Negative		
1965–1970	274	1.5
1971–1974	213	3.8
1975–1978	263	0.8
Total	750	1.9
Node Positive		
1965–1970	219	5.0
1971–1974	134	5.3
1975–1978	185	3.2
Total	538	4.5
All Patients		
1965–1970	493	3.0
1971–1974	347	4.3
1975–1978	448	1.8
Total	1288	3.0

In an effort to determine whether disease-free survival rates improved by year of treatment independently of other known prognostic variables, multivariate analysis for all patients treated from 1965 to 1978 was done (Table 14). The list of covariates was limited deliberately to those known to be most predictive of survival (pathologic/clinical node status, and tumor size). In both univariate and multivariate calculations, year of treatment exerts a small but significant effect. This may reflect the benefit of treatment modalities (such as systemic adjuvant chemotherapy) added in more recent years, although when the analysis was repeated for the 1965 to 1970 and 1971 to 1978 groups separately (using number of positive axillary nodes rather than highest level), year of treatment was unrelated to survival, indicating the relatively borderline significance of this finding.

Discussion

This study was undertaken to examine the 'bottom line' in a large group of patients treated for operable breast

TABLE 12. *Local Recurrence by Stage*

	Clinical		Pathologic	
Stage/Years	No. Patients	Local %	No. Patients	Local %
Stage I				
1965–1970	225	3.1	165	1.8
1971–1974	178	2.2	138	2.9
1975–1978	270	1.5	201	1.0
Total	673	2.2	504	1.8
Stage II				
1965–1970	245	2.4	305	3.3
1971–1974	139	5.8	188	4.8
1975–1978	148	1.3	223	1.8
Total	532	3.0	716	3.2
Stage III				
1965–1970	23	8.7	23	8.7
1971–1974	30	16.7	21	10.0
1975–1978	30	6.7	24	8.3
Total	83	9.9	68	9.2

TABLE 13. *Survival from Date of Recurrence by Site of First Recurrence*

Years	No. Patients	5-year Survival %	
	Local only		
1965–1970	15	44	
1971–1974	15	35	
1975–1978	8	86	(p = 0.37)
Total	38	46	
	Local/distant or distant only		
1965–1970	153	12	
1971–1974	82	11	
1975–1978	83	47	(p < 0.0001)
Total	318	19	
	All patients failing treatment		
1965–1970	168	15	
1971–1974	97	15	
1975–1978	91	47	(p = 0.0001)
Total	356	21	

cancer with radical surgery during a 13-year period by one surgeon at one institution. Did changes in patient population, tumor factors, and pattern of local/systemic therapy affect 10-year survival rates and local control?

Progressively earlier stage of disease was a consistent finding throughout the study, and perhaps the greatest influence on the improved survivals noted. Mean tumor size decreased steadily and is part of a trend at Memorial Hospital: mean tumor size was 3 cm in 1194 patients (from 1940 to 1943),[8] 3 cm in the first 70 patients having extended radical mastectomy (in the early 1950s),[9] 2.5 cm (from 1965 to 1970), and 2.2 cm (from 1975 to 1978). Median was constant at 2 cm (from 1965 to 1978), indicating fewer patients with large tumors in recent years. Pathologic axillary node involvement decreased comparably: 62.6% positive (1940 to 1945),[10] 55.7% (1950 to 1955),[9] 44% (1955 to 1964),[11] 44% (1965 to 1970), and 41% (1975 to 1978). These data indicate a leveling off both in tumor size (which did nevertheless decline significantly from 1965 to 1978) and in frequency of axillary involvement (which did not). We hope that the more widespread and frequent mammographic screening of the 1980s will result in still earlier stage at diagnosis.

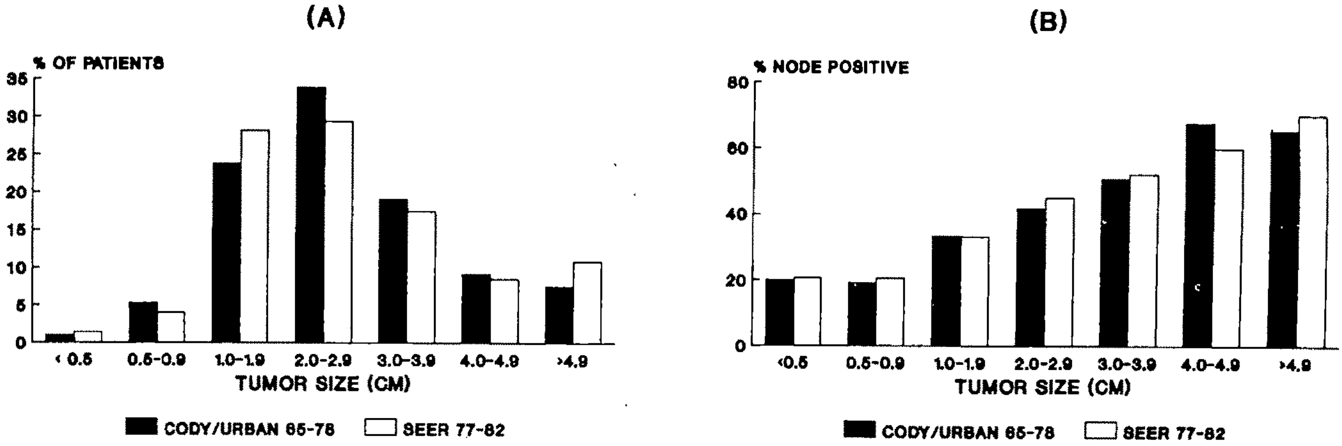
Recent data from the SEER Program of the National Cancer Institute correlate tumor size and axillary node involvement in 24,170 breast cancer patients (treated nationwide from 1977 to 1982), and indicate a linear relationship between the two.[12] The present data confirm this finding and indicate both by size distribution and extent of axillary node involvement (Figs. 3 and 4) that the patients in this study are comparable to those treated for operable breast cancer nationwide (of whom the SEER data represent about 10%). A frequent explanation for the excellent results reported from single-surgeon or single-institution studies has been the selection of an unusually favorable patient population. The patients in this study are, in fact, representative of the average breast cancer patient treated nationally, especially for the vast majority (94% to 96% in this series) with T1 or T2 disease; the T3 (stage III) patients in this study, 4% to 6% of the total, by contrast comprise a more favorable group than the T3 patients, 10.9% of the total, in the SEER data (Fig. 4).

Primary surgical treatment changed dramatically during the period studied. In 1965, 89.7% of patients underwent RM or ERM. By 1978, 73.8% had MRM. The trend away from RM and ERM and toward MRM parallels that noted in the 1982 National Survey taken by the American College of Surgeons (ACS),[13] in which the use of RM decreased from 48% to 3% in the years 1972 to 1981, while MRM increased from 28% to 73% during the same time period. Overall the pattern of surgical treatment nationwide was considerably less radical than in the present series. Nationally only 0.6% to 1.1% of patients had ERM, and 10.6% to 12.4% had lesser procedures than MRM (either total mastectomy alone or partial mastectomy). This trend has undoubtedly continued, particularly in view of the results of randomized studies from Milan (10-year follow-up)[1] and the NSABP B-06 trial (8-year follow-up)[14] indicating the efficacy of local excision, axillary dissection, and radiotherapy for patients with favorable disease (*i.e.*, smaller tumors and clinically negative axillae). While in other prospective randomized studies Veronesi and Valagussa[15] have questioned the benefit of ERM compared with RM, conflicting data from Lacour[16]

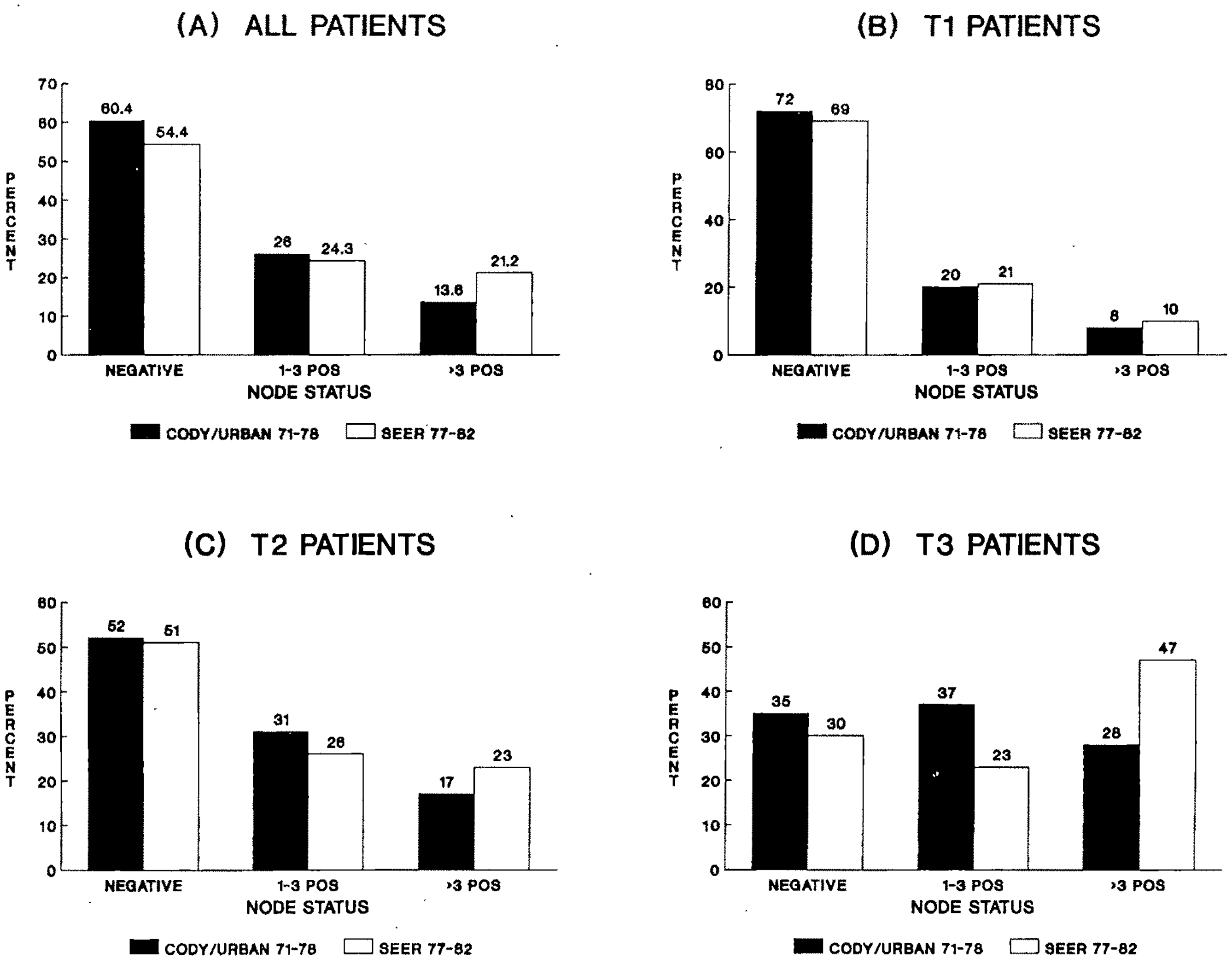
TABLE 14. *Univariate and Multivariate Analysis Determinants of NED Survival*

Variable	Chi Square	p
	Univariate	
Highest level positive	137	<0.00005
Clinical node status	51	<0.00005
Tumor size (pathologic)	48	<0.00005
Year treated	9.5	0.002
	Multivariate	
Highest level positive	137	<0.0005
Tumor size (pathologic)	24	<0.0005
Clinical node status	9.3	0.017
Year treated	5.7	0.002

NED, no evidence of disease.



FIGS. 3A and B. Comparison of patients in this study (1965–1978) with the SEER study (1977–1982),[12] by (A) size distribution and (B) percentage node positive by tumor size.



FIGS. 4A–D. Comparison of patients in this study (1971–1978) with the SEER study (1977–1982),[12] by extent of nodal involvement for (A) all, (B) T1, (C) T2, and (D) T3 patients.

and Ferguson[17] demonstrate a role in the subset of patients most likely to have involved internal mammary nodes: Lacour found that for patients with inner quadrant, axillary node-positive lesions, the 15-year NED survival rate was markedly better with ERM than RM (44% *versus* 25%; $p = 0.05$), and Ferguson found that for inner quadrant tumors, his personal 10-year overall survival rate for ERM surpassed RM significantly (86% *versus* 60%, $p = 0.025$). In the present study the trend toward less radical surgical treatment has not adversely affected either local recurrence or long-term survival rate. Currently in this practice, patients are treated most frequently with MRM (65% to 70%), breast conservation (25% to 30%), RM (about 5%), and ERM (rarely).

Postoperative radiotherapy was used with decreasing frequency throughout this study, from 42% (from 1965 to 1970) to 27% (from 1975 to 1978), again parallel to trends in the 1982 ACS survey.[13] Radiotherapy was given selectively for various indications: (1) positive axillary nodes, particularly at levels II and III; (2) large, locally extensive or medially placed primary tumors; or (3) biopsy-proved internal mammary node metastases (in patients not having ERM). Most frequently a 'hockey stick' portal was used, treating internal mammary and supraclavicular nodes. Few patients received full chest-wall radiation (usually those with the largest tumors). Because complete axillary dissections were performed, radiation to the axilla was rare. In all cases radiation was used to maximize local control in patients at greatest risk of having residual microscopic local/regional disease. Randomized trials of postmastectomy radiotherapy, as recently reviewed by Harris and Hellman[18] and, in a meta analysis, by Cuzick et al.,[19] clearly demonstrated improved local control but equivocal survival benefit (perhaps in the range of 5%) for treated patients, presumably because the fraction of patients with residual local disease and without occult systemic metastasis after mastectomy is relatively small. Recent thought has increasingly emphasized the eradication of occult residual disease by adjuvant chemotherapy, although this modality is probably less effective than radiotherapy in preventing local recurrence.[18] The decreased frequency of postoperative radiotherapy from 1965 to 1978 in this study resulted in neither an increase in local recurrence nor a decrease in survival. Our current practice is to give postmastectomy radiotherapy after completion of chemotherapy to patients with biopsy-proved internal mammary node disease or more locally advanced cancers (stages III to IV, including inflammatory).

The impact of adjuvant chemotherapy, begun in 1975 following the reports of Bonnadonna et al.,[20] is difficult to determine from these data, primarily because the indications for treatment were still evolving at the time. The most striking survival improvement in the 1975 to 1978 group was within the subset of 32 premenopausal/one to three node-positive patients (7% of the entire group), precisely those patients found in controlled trials to benefit most from chemotherapy; however only one third of these 32 patients actually received chemotherapy after operation (Table 3). Why so few? Possible explanations include (1) a relative scarcity of supportive randomized trial data at the time, (2) short follow-up periods for patients treated in trials, (3) the possibility that chemotherapy was simply delaying recurrence without affecting overall survival, and (4) the perceived need for 12 to 24 months' total treatment. Since 1978 the criteria for adjuvant chemotherapy have become much clearer, with a trend toward treatment of many more premenopausal patients, ER-negative postmenopausal patients, and node-negative patients with additional risk factors.

Most intriguing is the suggestion in Table 13 that patients from 1975 to 1978 failing treatment survived longer from date of recurrence than did patients in earlier years. If this finding of a twofold prolongation of median survival is not artifactual, a clear implication is that multidrug chemotherapy (also begun in the mid-1970s) for recurrent disease may have exerted a significant survival impact. Unfortunately sufficient information about the treatment of all patients with recurrent disease was not available to address this issue in greater depth. Despite the enormous effort and expense devoted to the treatment of recurrent breast cancer, surprisingly few studies address the survival benefit of such treatment; Ross et al.[21] compared survival from date of recurrence in patients treated at the M.D. Anderson Hospital in the 1970s (using chemotherapy) with historical controls (using hormonal measures), and demonstrated only a 9- to 12-month improvement in median survival.

The overall and disease-free survival data in this study clearly demonstrate that the above trends in primary breast cancer treatment have not compromised either 10-year cure or local control of disease. Ten-year disease-free survival improved significantly for all patients, node positives, node negatives, and patients with either clinical or pathologic stage II disease. Multivariate analysis suggests (with the caveats noted above) that, even when controlled for pathologic stage (extent of nodal disease and tumor size), survival rate improved by year of treatment. Local-only recurrence at 10 years was 3% for all 1288 patients (with local-distant recurrence at 2%) and did not increase in recent years, despite fewer radical operations and less frequent radiotherapy.

Every patient in this series was treated with the 'Halsteadian' premise that a meticulous and thorough local treatment, individualized for each patient's disease and with the constant goal of maximizing local control, would yield superior long-term survival rates. This assumption cannot be proved true despite the excellent results observed. Conversely Fisher[22] has hypothesized that because most breast cancers are systemic from the outset, variations in local treatment (and local control) are unlikely to affect survival. The equivalent long-term survival rates among the three node-negative and two node-positive arms of the NSABP B-04 trial[2] are consistent with this premise, although the survival rates throughout (particularly for node-positive patients) are disappointingly low. The Halsteadian and Fisher hypotheses are not mutually exclusive and should be seen as complementary aspects of the same problem. Efforts to improve results further in operable breast cancer must seek to combine the systemic treatment of those patients most likely to have occult metastases, with an equally aggressive pursuit of local control. Whatever small survival increment is gained by systemic adjuvant therapy will otherwise be nullified by inadequate local treatment.

Since 1978 the local and systemic treatment of breast cancer has continued to evolve rapidly. Breast conservation has become well established as a treatment option for patients with early disease. The Milan trial (1973 to 1980)[1] comparing quadrantectomy, full axillary dissection, and radiotherapy with RM (± CMF), limited to patients with T1N0 cancers, showed no overall or disease-free survival differences between the two arms at follow-up now exceeding 10 years. The NSABP B-06 trial (1976 to 1984)[14] comparing total mastectomy, local excision-RT, and local excision alone (all done with axillary dissection) showed no overall or disease-free survival difference between total mastectomy and local excision-RT at 81 months mean follow-up. Of particular note, however, was the 39% local relapse rate in patients treated by local excision without radiotherapy; the 8-year disease-free survival rate in this group was 5% worse ($p = 0.01$) than in patients treated with local excision-RT. A further cautionary note is sounded by the long-term results of the first and second Guy's Hospital trials[23] comparing RM with local excision and 3500 to 3800 R radiotherapy (inadequate by current standards). The first trial (1961 to 1971) showed equivalent survival rates for patients with stage I disease (despite more local recurrences in the local excision group), but a marked advantage both in local recurrence and long-term survival rate for RM in stage II patients. The second trial (1971 to 1975), limited to stage I patients treated only by experienced full-time surgeons in a dedicated breast cancer unit, demonstrated less frequent local recurrence ($p < 0.000009$) and better survival ($p < 0.002$) for RM. When adjusted for tumor size, this advantage was limited to patients with T1 lesions, precisely the group chosen most often at present for breast conservation. Even with full doses (4500 to 7500 R) of radiotherapy to the involved breast, local relapse after breast conservation for early cancers (in data pooled from major centers) has averaged 1% to 2% per year for the first 15 years after treatment.[24] Another prospective randomized trial by Maddox et al.[25] (1975 to 1978) compares RM and MRM in 311 patients with stages I to III breast cancer. Ten-year local relapse was 6% for RM and 11% for MRM ($p = 0.04$). Overall 10-year survival rates did not differ 'significantly' (71% *versus* 64%, $p = 0.14$), but among patients with node-positive T2 and all T3 tumors there was a marked survival advantage for RM (59% *versus* 38%, $p = 0.05$). The above studies suggest a clear relationship between adequacy of local control and long-term disease-free survival, although the threshold beyond which local recurrence begins adversely to impact overall and disease-free survival is unclear. The advantage for radical surgery is clearest in patients with more locally advanced disease and may be undetectibly small with early cancers. The proportion of cancers for which breast conservation is appropriate remains controversial, although as the fraction of T1N0 patients increases through earlier detection, this number should increase correspondingly.

The 1288 patients in this series may be among the last to be treated exclusively by radical surgery: RM, ERM, or MRM. The results are reported in sufficient detail to allow comparison with patients staged clinically or pathologically, or grouped by age and extent of axillary node involvement. Changing treatment patterns from 1965 to 1978 did not compromise outcome and, in fact, overall results improved. We hope current studies of patients treated in this practice since 1978 will continue to demonstrate the same result.

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Surgical Prophylaxis of Malignant Melanoma

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A review of a 14-year experience with prophylactic pigmented skin lesion removal is presented. Data obtained during a 4-year interval of this 14-year experience is analyzed specifically. During this 4-year interval, 250 patients with melanoma were seen. Of these patients, 75 with a history of stage I (localized) melanoma and three patients with stage II (history of controlled regionally metastatic melanoma) underwent removal of multiple skin lesions on a prophylactic basis. Of the removed lesions, 28% showed hyperplasia, atypia, dysplasia, or melanoma. Nine unsuspected *in situ*, or level I melanomas, and three unsuspected invasive melanomas were removed from these 75 melanoma patients while excising lesions prophylactically during the 4-year interval. It is estimated that four to six additional melanomas were prevented by excision of precursor lesions. During the same 4-year interval, an additional 112 of approximately 1000 patients without a previous history of melanoma underwent prophylactic lesion removals. In 31% of the 112 patients, there was a history of melanoma in a first-degree relative. In 22% of the removed lesions there was hyperplasia, atypia, or dysplasia. Three cases of melanoma *in situ* were detected and it is estimated that an additional three to five cases of melanoma were prevented. Atypical findings occurred in 71, or 63%, of the patients biopsied, which represented 7% of the approximately 1000 patients screened. During the 4-year interval, an average of 17.7 lesions were removed from each of the 190 melanoma and nonmelanoma patients undergoing prophylactic skin lesion excision. This was accomplished in one to four sessions per patient. This average reflects only those patients who underwent one excision or more and does not include those patients treated without operation. When including the nonoperated patients screened during this interval, the average number of lesions removed was 2.7 per patient. Death from new melanomas was prevented during the 14-year period of this study as evidenced by the fact that no patient died or developed metastatic disease from a cutaneous melanoma that was not apparent or known about at the time of first examination.

THE ORIGINAL DESCRIPTION of melanoma in the English language was by Norris in 1820.[1] He described a 59-year-old man who on February 6, 1817 'applied to me in consequence of the inconvenience he felt from a tumor, situated nearly midway between the umbilicus and the pubis. He told me that there had always been a mole exactly on the same spot and that, nine months ago, the skin around this congenital mark assumed a brownish hue and that from the part thus discolored a tumor began to arise.' Later in his course the patient experienced 'increase of restlessness, cough, and difficulty of breathing, until death closed his miserable existence.' On postmortem examination he had disseminated melanoma metastases. One has the impression that earlier removal of his infraumbilical lesion may have prevented his death.

It has been recognized since 1897 that the melanocyte, which is the cell of origin of melanoma, is also the cell of origin of pigmented, benign lesions.[2] The production of melanin by melanocytes in normal skin affords protection from sun exposure, as melanocytes replicate in response to ultraviolet light.[3] Melanocytes are also a component of 'nevi,' defined as 'malformations' of the skin containing a 'local excess' of components of normal skin,[4] notably melanocytes, where they are referred to as 'nevus cells.' In melanocytic nevi the melanocytes, or nevus cells, demonstrate abnormalities affecting their growth population density, morphology, and melanogenesis.[5] Melanocytic nevi may be subdivided into common blue nevi, cellular blue nevi (whose slight malignant potential has been considered by us and others[6,7]), congenital nevi, and acquired nevi. Acquired nevi, being quantitatively the most important, generally are thought to begin as junctional nevi. These are so named because of the proliferation of melanocytes ('nevus cells') at the junction of the epidermis and dermis, along the basal layer of the epidermis. Nevus

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cells proliferate within the epidermis and then drop into the dermis where they mature to form the intradermal nevus. The compound nevus is a transitional phase in which both junctional and intradermal components are present.[8]

This intraepidermal melanocytic proliferation, or 'junctional activity,' has been of particular concern in relation to melanoma development and the junctional nevus has been regarded as a possible melanoma precursor.[9–13] Nevi of the palms, soles, and genital region are thought to be almost always junctional in nature, and although it was recognized that most junctional nevi would remain benign, their prophylactic excision was recommended for diagnosis and for prevention of melanoma.[11–13]

Pack et al.[14] had more than 3000 cases of melanoma in a personal series. He and Davis thought that 90% of melanomas arose in pre-existing junctional nevi and recommended prophylactic removal of pigmented skin lesions under many conditions, including deeply pigmented nevi in blond or redheaded individuals or individuals who have a sandy complexion and who freckle on exposure to sunlight. He noted that whereas only 11% of the American white population has this coloration, more than 65% of patients with melanoma have this type of skin. Nevi subject to repeated irritation or infection, or showing increase in size or pigmentation, were recommended for prophylactic removal.[11] Schwartz,[15] in his textbook of surgery, discussed melanoma development from the junctional component of nevi and recommended, without reservation or qualification, that lesions considered to be junctional nevi should be excised.

The description of dysplastic nevi and the familial atypical multiple mole syndrome[8,16–23] emphasized the familial nature of melanoma and described characteristics of precursor dysplastic lesions associated with increased risk for melanoma development. Titus-Ernstoff, Duray, and coworkers[24] recommended that melanoma patients may benefit from prophylactic excision of nevi suspicious of being dysplastic. Greene indicated that prophylactic removal of dysplastic nevi was warranted for lesions located in the scalp, in immunosuppressed patients, in cases in which many atypical nevi were present on clinical examination, or where the presence of preneoplastic lesions created serious emotional difficulty.[25] He also indicated that because the dysplastic nevus syndrome was recognized only recently, its optimal management is still being determined and definitive recommendations must await additional follow-up. Ackerman[26] objected to the term 'melanocytic dysplasia' and questioned the significance of dysplastic nevi. However he acknowledged that if sporadic or familial dysplastic nevi were truly common precursors of malignant melanoma, as maintained by other workers and by the National Institutes of Health Consensus Development Conference on melanoma precursors,[27] then 'it becomes mandatory for clinicians not only to recognize these lesions but also to remove them prophylactically as well.'[26]

The results of an active approach such as that mentioned by Pack, Schwartz, Titus-Ernstoff, and Ackerman have not been described previously, especially in the dysplastic nevus era of the past decade. The purpose of this study was to review the results of a 14-year experience during which an active role in pigmented lesion removal was undertaken. This was an experience that began around the time of the descriptions of the familial mole syndromes and the re-emphasis on precursor lesions in melanoma development. Around the same time we reported the efficacy of individual lesion destruction as a method of control of locally metastatic melanoma.[28] In that study, through the individual destruction of thousands of melanoma satellite lesions with intralesional injections of the chemical dinitrochlorobenzene, some patients with dozens of metastatic melanoma lesions were rendered free of disease and have remained so to the present time, more than 13 years later. In the current study we again used an 'individual lesion destruction' approach, directed against selected nonmalignant lesions. This was intended as a prophylactic maneuver in light of evidence that melanoma development often proceeded through a phase in which simple excision of a precursor lesion could prevent development of a melanoma that otherwise would progress to an untreatable, fatal condition with distant metastases.

The current study concentrated on lesions removed prophylactically, rather than on lesions removed from patients referred because of an apparent melanoma. We determined the proportion of prophylactically removed lesions showing melanocytic atypia, hyperplasia, or dysplasia. We tried to assess the efficacy of multiple skin lesion removal as a method to prevent new primary melanomas in patients with and without a history of previous melanoma. In addition, whereas previous studies presented statistics regarding dysplasia in melanoma patients, no attempt was made previously to present lesion excision data for stage I (localized) melanoma patients as a subgroup. It is in these stage I patients that prophylactic lesion removal to prevent a potentially lethal second primary melanoma may be of greatest benefit, as compared to prophylactic lesion removal in melanoma patients with a history of stage II (regionally metastatic) or stage III (disseminated) disease.

Materials and Methods

All of the pigmented lesion patients in this study were cared for by a single surgeon (MH Cohen) during the past 14 years. When specific numeric data are recorded, they were obtained from a record review of patients operated on during a 4-year interval around the middle of the overall 14-year period. A total of 250 melanoma patients were seen during the 4-year time period. All of these patients were postpubertal when first diagnosed with melanoma. Seventy-eight of these 250 melanoma patients underwent prophylactic pigmented lesion removal, as will be discussed. In addition approximately 1000 patients without a history of melanoma were evaluated, of whom 112 also underwent prophylactic lesion removals during the same 4-year interval.

Patients undergoing removal of one to three skin lesions typically had the procedure performed in an office setting. Those having more lesions removed were operated on in an out-patient surgery facility, under local anesthesia, using 0.5% Xylocaine® (lidocaine HCl) with epinephrine 1:100,000 (Astra Pharm-Products Westborough, MA). We limited the amount of lidocaine to 7 mg/kg of body weight, which, in a 70-kg patient translated to approximately 500 mg, or 100 mL of a 0.5% solution. The addition of a sodium bicarbonate solution to the Xylocaine® solution resulted in a marked reduction or elimination of the discomfort associated with tissue infiltration. This was accomplished by adding 25 meq of sodium bicarbonate (25 mL of a standard 8.4% solution) to each 50 mL of Xylocaine® solution. This formulation essentially eliminated the pain of injection without causing cloudiness or precipitate in the mixture.

The excisions were carried out by surgical removal of ellipses of skin with a #15 scalpel blade. The plane of excision was usually through the white fibers of the deep (reticular) dermis. Skin lines of tension were respected, although the primary concern in incision placement was the shape and orientation of the lesion. Hemostasis was achieved through electrocoagulation. Closure was carried out with 4–0, 5–0, and sometimes 6–0 nylon interrupted sutures. Intradermal absorbable 6–0 sutures also were sometimes used. Each lesion was numbered and its location named as it was excised. A location frequently was designated as being superior or inferior to a preceding lesion. In the case of multiple back lesions, the lesion's relationship to a particular vertebra, or scapula or other bony landmark was useful in naming. All lesions were pathologically examined grossly and microscopically. Some of the lesion removals in this study were at the request of the patient, without concern that the lesions may harbor melanocytic hyperplasia, atypia, or dysplasia. However most lesions were selected for prophylactic removal primarily by the presence of apparent significant junctional activity, as suggested by depth of pigmentation, size of the lesion, irregularity of the periphery of the lesion, variability of pigmentation within the lesion, or elevation above the skin surface. The location of the lesion, the personal and family history of the patient, and the history of the lesions themselves also were noted. Many of the lesions were considered to be potentially harboring microscopic evidence of lentiginous or melanocytic hyperplasia, melanocytic atypia, or dysplasia. These microscopic patterns, which frequently were not distinguishable from each other on gross visual examination, may be on a biologic continuum, and were grouped together in the statistical analyses in this study.

Lesions with 'melanocytic hyperplasia' demonstrated, on microscopic assessment, an increase in the expected number of melanocytes appearing at the dermoepidermal junction. The melanocytes were individual rather than in nests, and were approximately equidistant from each other. The cells may have been slightly enlarged but there was no significant cytologic or nuclear atypia and mitoses were not found. If the rete ridges were elongated, the hyperplasia was termed 'lentiginous.'

Lesions demonstrating 'atypia' or 'atypical melanocytic hyperplasia' showed an increase in the number of melanocytes, predominantly at the dermoepidermal junction, with a variable degree of cytologic or nuclear atypia. Mitoses sometimes were observed and there was a tendency toward melanocytic crowding.

The term 'dysplasia' or 'dysplastic nevus' implied both architectural and cytologic changes. The epidermis revealed elongation of rete ridges, along the sides and tips of which were found unevenly spaced, usually mildly atypical melanocytes. There was a tendency for the formation of somewhat irregular nests that might 'bridge' from one rete to the other. In the dermis lamellar fibroplasia, foci of chronic inflammation, and capillary proliferation could be found. The melanocytic atypia usually was minimal and could assume either the more common lentiginous pattern or the epithelioid pattern.

Patients with pigmented lesions seen during the 14-year period of this study generally fell into several categories and became subjects of the study at different points. Some patients were referred because a lesion was thought to represent a melanoma by the treating physician. If the lesion was a possible primary melanoma, typically it was excised on the first office visit. A narrow rim of normal-appearing, full-thickness skin was taken with the lesion and the wound was sutured closed primarily. These excisions were not included in the data to be presented.

After biopsy, sites of invasive melanomas were excised widely with a 3-to-4–cm margin, which usually required a split-thickness skin graft for adequate closure. Narrower margins were taken on thinner, less invasive lesions. These melanoma re-excisions also are considered for the purposes of this paper to represent therapeutic rather than prophylactic excisions and are not included in the subsequently presented statistics.

Melanoma patients were staged by physical examination, lung tomography, and liver–spleen radionuclide scanning. Patients with disease apparently confined to the local site were potential candidates for prophylactic lesion removal. A portion of these patients were selected for skin excisions, as will be discussed. These excisions usually were carried out within the first year following melanoma wide excision.

Melanoma patients were scheduled for monthly follow-up appointments the first year or two, then every 2 or 3 months or more, depending on the nature of the original melanoma and the patient's tendency to form atypical or hyperplastic lesions in other locations.

During the 4-year time interval for which statistical analysis was completed, 112 patients, from a group of approximately 1000 patients without a personal history of melanoma, also were selected for skin lesion removals. The data on these patients are tabulated separately. Patients undergoing skin lesion removal without a history of melanoma were seen at 3- to 6-month intervals, depending on the nature of their gross and microscopic findings.

Almost all the patients in these studies were Caucasian and were counselled regarding sunscreens and solar exposure. A few patients during the 14-year period underwent more than one round of excisions, depending on the histologic characteristics of the lesions removed, their tendencies for lesion formation, and their compliance with solar protection programs.

Results

Two hundred fifty patients with a history of melanoma and approximately 1000 patients with pigmented lesions without a history of melanoma were evaluated during a 4-year interval. Of the 250 melanoma patients, 90 had or developed stage II (regional) or stage III (disseminated) melanoma. Eighty-seven of these 90 patients were excluded from lesion removal because of their history of metastasis, although three well-controlled stage II patients underwent lesion removal. The main application of prophylactic lesion removal in melanoma patients was in patients with a history of stage I melanoma. One hundred sixty of the 250 melanoma patients had stage I disease and thus were considered potential candidates for lesion removal (64% of the 250 melanoma patients). Of these 160 stage I patients, 85 did not undergo lesion removal in the 4-year interval described because their lesions did not meet the previously mentioned criteria for excision. The remaining 75 stage I melanoma patients (47% of the stage I patients or 30% of the entire 250 melanoma patient group) had 1591 lesions removed, of which 445, or 28%, showed hyperplasia, atypia, dysplasia, or melanoma. On a per patient basis, of the 75 stage I patients undergoing lesion removal, 60 (80%) showed hyperplasia, atypia, dysplasia, or melanoma in the lesions removed. In addition three patients with a history of apparently well-controlled stage II melanoma underwent excision of 39 lesions with similar findings of hyperplasia, atypia, or dysplasia in nine lesions.

The unsuspected melanomas removed as a result of prophylactic skin lesion removal in patients with a history of previous melanoma included three invasive melanomas and nine *in situ*, or level I melanomas. In addition it was estimated that one melanoma is prevented by the removal of each 11 to 80 dysplastic lesions in a familial dysplastic setting[25,29] or 83 dysplastic lesions in a nonfamilial setting.[29] Based on extrapolation from these data, attempts were made to estimate the number of additional melanomas prevented by our prophylactic excisions in the melanoma patients. In so doing, we accounted for the fact that our patients in this group all had a melanoma personal history, which placed them at a higher-than-average risk for melanoma development, compared to the general population of patients with dysplastic skin lesions.[29] Conversely included in our statistics are lesions with hyperplasia and atypia, which may be at less risk for early melanoma development, as compared to lesions with dysplasia. On balance, however, it is estimated that an additional four to six melanomas were prevented by the removal of 433 atypical, hyperplastic, or dysplastic pigmented lesions in these 75 stage I melanoma patients.

In summary, in the 250 melanoma patients seen in a 4-year period, 87 were excluded from prophylactic lesion removal because of the presence or history of metastatic disease. Eighty-five stage I patients were excluded because physical examination did not reveal apparent significant abnormalities in their nevi. Seventy-five stage I patients and three stage II patients underwent removal of a total of 1630 lesions. Eighty per cent of these patients showed abnormalities in the pigmented lesions removed. Twelve unsuspected melanomas were removed and it is estimated that approximately four to six others were prevented by the removal of precursor lesions.

During the same 4-year interval, approximately 1000 patients without a personal history of melanoma were seen for pigmented skin lesions, of whom 112 underwent excisions. Of the 1731 lesions excised from these patients, 377 or 22% showed hyperplasia, atypia, or melanoma *in situ* (three cases). Of the 112 patients undergoing lesion removal, 71 patients (or 63%) demonstrated these findings, which were present in 31% (377 of 1208) of the lesions removed from these 71 patients. In addition to the three melanomas *in situ* that were excised, it is estimated that three to five melanomas were prevented in this group of patients by excision of potential precursor lesions.

Twenty-one (or 30%) of the 71 patients with hyperplasia, atypia, dysplasia, or melanoma *in situ* had a family history of melanoma in a first-degree relative. Among the lesions removed from patients with a family member with melanoma, 78 of 342, or 23%, demonstrated hyperplasia, atypia, or dysplasia. Forty-one (112 minus 71) patients without a personal history of melanoma underwent 523 lesion excisions without hyperplasia, atypia, or dysplasia being reported in the removed lesions. Fourteen (or 34%) of these 41 patients were first-degree relatives of patients with melanoma.

Considering together the lesion removals mentioned in the 78 melanoma and 112 nonmelanoma patients, approximately 25% (831 of 3361) were hyperplastic, atypical, dysplastic, or melanoma *in situ.* On average 17.7 lesions were removed from each patient undergoing skin lesion surgery. In two patients this was accomplished in four sessions, and in the other cases between one and three sessions were required. Considering that 250 melanoma patients and approximately 1000 nonmelanoma patients were seen during this period, the average number of lesions removed per patient screened (including operated and nonoperated cases) was 2.7 lesions per patient.

As mentioned, the statistics reported throughout this study included lesions removed at the patient's request. In addition it should be mentioned that the 'negative' lesions include basal and squamous cell carcinomas, actinic keratoses, cysts, lipomas, and other lesions that are not considered to be potential forerunners of melanoma. However most of the 'negative' lesions were junctional, compound, and intradermal nevi not demonstrating melanocytic hyperplasia, atypia, or dysplasia on microscopic observation.

More than 90% of the lesion removals were performed in the out-patient surgery clinic at a single institution. Most of the lesions were read by a single pathologist with special training in dermatopathology.

In the 14 years of this study, no patient developed recurrence or death from a primary cutaneous melanoma not apparent or known about at the patient's first visit. This was true among the patients who presented with a primary melanoma and among the patients with and without a family history of melanoma who underwent lesion removals.

Discussion

An element of confusion exists in the field of pigmented skin lesion treatment. This is in part due to the terminology differences for a group of lesions variously described as active junctional nevi, nevi with melanocytic atypia, dysplastic nevi, and melanoma *in situ.* Different pathologists may read the same slides differently and sometimes the same pathologist may read the same slide differently at different times. This is an observation reminiscent of our previously reported observation regarding assessment of Clark levels of invasion in melanoma. When the same pathologists reviewed the same melanoma slides several years apart, significant variations in assessment occurred.[30]

Sometimes it has been difficult to determine the biologic significance of some of the microscopic observations associated with pigmented lesions. For example some authors have raised questions regarding the significance of apparent dysplastic nevus elements contiguous with some melanomas. Maize and colleagues[31] questioned whether these dysplastic nevus elements might have been induced by the melanoma as a type of 'field effect.' On the other hand, the dysplastic nevus elements may have arisen independently in synchrony with the melanoma, or the dysplastic lesion may have been a formal precursor. Maize[31] stated that most melanomas did not contain histologic elements of precursor dysplastic nevi. However, as pointed out by Pack,[11] it is difficult for a pathologist to determine conclusively that a pre-existing, benign, junctional lesion was not previously present at a site where melanoma developed because the melanoma development is capable of obliterating evidence of the pre-existing nevus as the melanoma advances before its biopsy. In addition, in case of very early melanomas, there is circumstantial evidence that the lesion was preceded by a pre-existing benign junctional lesion because of the morphologic similarity between melanomas and the intraepidermal hyperplasia of some nevi, and the observation of histologically borderline lesions.[32-34]

It has also been argued that nevi may become activated in patients with melanoma, resulting in a disordered growth pattern.[35,36] However this alone would not explain the presence of activated nevi in patients who have never had melanoma, who have no residual melanoma, or in whom the activated nevi precede the malignancy.

Should dysplastic lesions be removed or observed? At the National Institutes of Health Consensus Development Conference, it was concluded that the dysplastic nevus was not only a marker depicting that the patient was at increased risk for melanoma development but also that the dysplastic nevus itself was a precursor of melanoma.[27] Ackerman[26] disagreed with that conclusion but indicated that if a physician agreed that these nevi are indeed common precursors of melanoma, it would be 'mandatory' that they be removed prophylactically. The desirability of the removal of melanoma precursor lesions is based on the estimates that, whereas 0.7% of the general population will develop melanoma, the incidence reportedly increases to approximately 18% in those with dysplastic nevi, and approaches 100% in those who have dysplastic nevi and two family members with a history of melanoma.[29] Patients with dysplastic nevi were found to have an average of 10 dysplastic lesions per patient in the nonfamilial dysplastic nevus syndrome setting, and 10 to 75 dysplastic nevi in the familial dysplastic nevus setting. Evidence also indicates that when melanoma develops in patients with dysplastic nevus syndrome, it begins within the dysplastic lesions 67% to 94% of the time. This led to the conclusion that the removal of approximately 83 dysplastic nevi should prevent the development of at least one melanoma in the nonfamilial dysplastic nevus syndrome patient, and the removal of 11 to 80 dysplastic nevi should prevent the development of one melanoma in the familial dysplastic nevus syndrome patient.[25,29]

Greene, Clark, and coworkers[37] recommended managing dysplastic nevus syndrome patients generally by observation with whole-body photography (a little-used technique) and by selected removals. However they did indicate that prophylactic removal was justified, in their opinion, in patients with suspected dysplastic scalp lesions or unusually large numbers of atypical nevi. They also indicated that prophylactic dysplastic lesion excisions could be justified in immunosuppressed patients, in patients with emotional difficulty associated with the harboring of possibly preneoplastic skin lesions, or in patients who have limited access to appropriate medical follow-up.

Titus-Ernstoff and coworkers[24] suggested that patients with a history of melanoma might benefit from the removal of nevi suspicious of being dysplastic. Our studies indicate that if nevi suspicious for dysplasia are removed, some melanomas are probably prevented and early melanomas are diagnosed and treated at a stage when no local recurrence, distant metastases, or subsequent mortality ensued in a 14-year time period. Also in Titus-Ernstoff's study of 121 subjects, two cases of melanoma were detected as a result of biopsies performed for study purposes, although the lesions were not considered to be clinically suggestive of melanomas before the biopsies. We shared this type of experience. In addition, in approximately 20% of patients referred to us with biopsy-proved melanoma, the pathology report on the biopsy did not mention melanoma among the potential prebiopsy diagnoses. This was particularly true in the case of the less-advanced, nonpigmented, or lightly pigmented lesions. In most of these cases, the preoperative diagnosis was that of a benign lesion, such as keratosis or angioma. Basal cell carcinoma was the most common malignant prebiopsy misdiagnosis.

The arguments against a prophylactic excisional approach include scarring and increased expense as compared to conservative observational management, although the expense of whole-body photography or treatment of a developed or progressive melanoma can be significant. The argument also was made that melanomas detected or prevented by prophylactic excision also might have been detected later by a 'watch and wait' approach at a time when they might still be curable. However we have seen a significant number of patients in whom a watch and wait approach has resulted in the progression of a pigmented lesion to the point at which a presumably curable lesion progressed to become a lethal one. Besides these cases in which an ultimately lethal lesion was followed by the patient, or less frequently by a physician, there are cases in which a precursor lesion that could have been recommended for excision by a physician was never noticed by the patient who then saw no physician until the lesion became lethal. In these cases as well, early excision probably would have been curative.

Another argument against observational management of dysplastic nevi are the patients who are lost to follow-up. The length of follow-up for a patient diagnosed as having a dysplastic nevus is frequently only a few years, despite assiduous attempts at follow-up. Patients who undergo melanoma excision, while being more compliant in follow-up initially, may later be lost to follow-up as well.

In conclusion a balance must be struck between routine excisional biopsies of all pigmented lesions and overly conservative observational management. The data presented in this paper suggest to us that the benefits of early excisional biopsy of selected lesions outweigh the disadvantages of an early surgical approach, and that excisional biopsy of these lesions can decrease melanoma incidence and its associated morbidity and mortality.

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The Role of Bacteria in Pigment Gallstone Disease

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One hundred ten of nine hundred sixty consecutive patients who underwent surgery for gallstones (GS) had pigment stones (PS) (11.45%). Fifty brown PSs contained calcium bilirubinate, small amounts of cholesterol, and always calcium palmitate, were usually found in the common duct (96%), and were almost always associated with bile infection (98%) and diffuse erosion of the biliary mucosa. Fifty-one black PSs contained bilirubin polymers, calcium carbonate, and/or phosphate, seldom cholesterol, and never evident amounts of calcium palmitate, were mostly found in the gallbladder, and were associated with hemolysis or liver damage and with hyperplastic cholecystosis. Bile infection was found in 19.6% of cases, but bacteria were never found in the center of black PSs by scanning electron microscopy. Nine additional patients (8.2% of PSs, 0.9% of GSs) had concomitant black and brown PSs that were mostly found in the common duct and were always associated with bile infection. It is suggested that, even if PSs with concomitant black and brown material can be found, black and brown PSs greatly differ not only in pathogenesis but also in clinical behavior and treatment. In particular bacterial infection is important only in the pathogenesis of brown PSs while it plays no role in the initial formation of cholesterol, mixed or black GSs.

PIGMENT GALLSTONES ARE stones that contain large amounts of pigment material and little cholesterol.[1,2] They can be distinguished as black and brown stones simply on the basis of their color: brown stones are brownish yellow, soft, and show alternate dark and light layers in cross-section. They are said to occur principally in the Orient and usually are found in Western countries as recurrent common duct stones after cholecystectomy, even if they can be found in the common duct as well as in the gallbladder of old patients with no previous biliary surgery.[3,4] Brown stones consist mainly of calcium bilirubinate with little cholesterol and always contain calcium palmitate.[4] Infection has been documented at the time of stone removal in more than 90% of brown stones.[1-5]

Black pigment stones usually form in the gallbladder. They are generally small (less than 3 mm in diameter), irregular, with multiple spiculas. In cross-section they have a glasslike, featureless appearance. Black stones mainly contain bilirubin polymers, usually calcium carbonate or phosphate, seldom cholesterol, and never calcium palmitate.[3,4] They are rarely associated with bile infection. Patients in Western countries who have pigment gallstones usually have been considered to belong to this second category.[1,2] Previous studies suggested that bacteria play a key role in the pathogenesis of brown pigment stones.[1-10]

However the role that bacteria play in the formation of gallstones remains incompletely defined. Debate still continues as to whether other stones, in addition to brown stones, may be caused by bacteria.[8-13] In fact bacteria recently were identified in the majority of pigment stones and in the pigment portion of composite stones. Therefore bacterial infection has been considered a primary factor, not only in the pathogenesis of brown stones but also in the formation of black pigment gallstones.[8] Furthermore because bacteria were found by scanning electron microscopy on the surface of cholesterol gallstones, a possible role for bacteria in cholesterol stone formation also has been suggested.[11-13]

We documented for the first time that bile infection by *Escherichia coli* precedes rather than follows brown stone formation, and together with bile stasis is the main factor in their pathogenesis.[5]

In the present article, additional data on the relationship between bacteria and gallstones are reported that are derived from the study of 1000 consecutive patients who underwent surgery for biliary tract diseases.

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In particular, evidence is given that

(1) Brown and black pigment stones differ in composition and pathogenesis and should also require a different treatment.
(2) Sometimes, even if infrequently, pigment stones can be concomitantly black and brown. In these cases they behave as brown stones, *i.e.*, they are always associated with bile infection.
(3) Bacteria are crucial for the formation of brown stones, but not for that of black pigment or cholesterol stones.

Materials and Methods

The present data are part of a prospective study of 1000 consecutive patients who underwent surgery for bile tract diseases from 1980 to 1988. Gallstones were found in 960 cases. There were 895 patients with stones in the gallbladder. Two hundred one patients had stones in the common duct, which in 51 cases formed after cholecystectomy. In all of the patients, clinical, radiologic, and laboratory data were recorded. Histologic examination of the gallbladder was always performed. In some patients with biliary enteric anastomosis, specimens from the common duct also were examined. In addition to routine histology, scanning electron microscopy (ISI SX-25 SEM Pabisch, Milan, Italy) at 7 KV and transmission electron microscopy (Zeiss EM 109 TEM, Karl Zeiss, Oberkochen, FRG) at 80 KV of both gallbladder and common duct specimens also were performed in selected cases.[14,15] Bile specimens always were taken at operation. In patients with T tubes, bile specimens also were taken in the postoperative period. Bile pH analysis and bile culture always were performed. Stones obtained at operation were washed, dried, and photographed. After cross-section, they were classified according to previously reported morphologic criteria.[16,17] The analysis of stone composition was performed by x-ray diffractometry using a Siemens D 500 diffractometer (Siemens, Milan, Italy) and infrared spectroscopy, using a Perkin-Elmer 357 infrared spectrophotometer (Perkin-Elmer, South Pasadena, CA).[3-5] Identification of the various compounds was made by comparing the observed spectra and diffraction angles with those reported in the literature.[3,4,15-18] In a subset of patients, stone culture, stereomicroscopy, and scanning electron microscopy of stones (ISI SX-25 SEM Pabisch, Milan, Italy) were performed.[19]

Details of these methods have been reported elsewhere.[3-5,14,15,19]

In particular 15 patients with postcholecystectomy stones were included in the study both at cholecystectomy and at the second operation. Therefore they had stone and bile analysis in both cases.

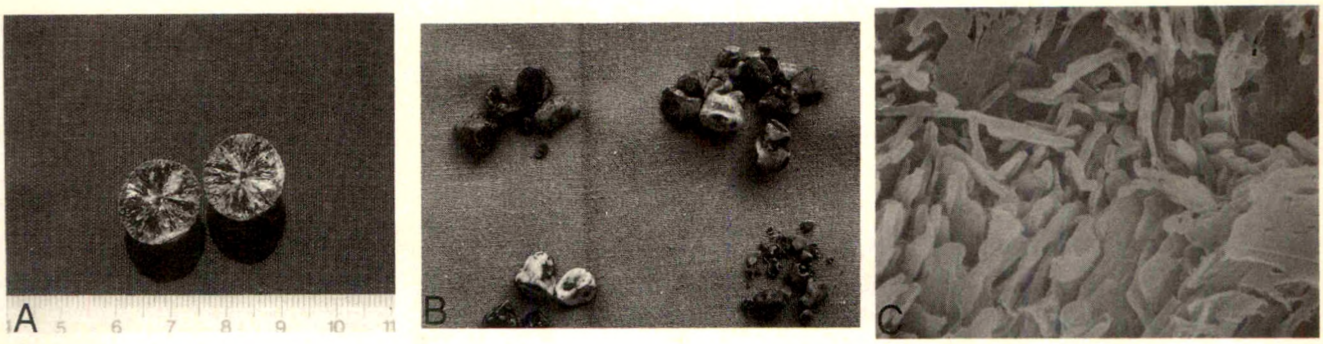
Results

Table 1 shows the data in the 960 patients with gallstones. There were 364 patients (37.9%) with ovoidal (or spheroidal cholesterol stones, 350 (36.5%) with faceted mixed stones (Fig. 1) and 110 with pigment stones (11.45%) (Figs. 1 to 4). Fifty had brown stones (5.2%) (Table 2, Fig. 2). Fifty-one had black pigment stones (5.3%) (Fig. 3). Nine had pigment stones that were concomitantly black and brown (0.93%) (Fig. 4). Seventy-

TABLE 1. *Classification of Gallstones According to Stone Morphology, Site, and Composition*

Stones	Type	n	Age	Sex		Site		Positive Bile Culture	Composition %			
				M	F	Gall Bladder	Common Duct		Chol.	Bil.	Carb.	Palm.
Cholesterol stones	Pure	364 (37.9%)	54.2	136	228	360 (98.9%)	20 (5.5%)	49 (13.5%)	90.3 ± 5.5	0.8 ± 1.5	1.0 ± 0.5	—
	Mixed	350 (36.5%)	58	95	255	331 (94.6%)	93 (28.6%)	70 (20%)	85 ± 10	2.5 ± 1.2	1.3 ± 0.7	—
Pigment stones	Brown	50 (5.2%)	73.2	23	27	16 (32%)	48 (96%)	49 (96%)	10.4 ± 6	51 ± 17	traces	23 ± 11
	Black	51 (5.3%)	58.8	22	29	50 (98%)	11 (21.6%)	10 (19.6%)	7.5 ± 4.7	61.8 ± 11.6	6.5 ± 6.0	—
	Black and brown	9 (0.9%)	74.3	6	3	2 (22%)	9 (100%)	9 (100%)	7.8 ± 4.0	55.4 ± 14.5	1.0 ± 0.7	12.5 ± 6.3
Combination stones		72 (7.5%)	56.5	20	52	66 (92%)	9 (12.5%)	29 (40%)	Various			
Other stones		64 (6.7%)	58	25	39	60 (93.7%)	11 (17.2%)	13 (20.3%)	Various			
Total		960	56.7	327	633	833	201	229				

Composition according to infrared spectroscopy and/or x-ray diffractometry (percentage of stones dry weight) Chol, cholesterol; Bil., calcium bilirubinate; Carb, calcium carbonates (calcite, aragonite or vaterite); PALM, fatty acid calcium salts (mainly calcium palmitate).



FIGS. 1A–C. Ovoidal cholesterol (A) and faceted mixed stones (B). Scanning electron microscopy (C): no bacteria.

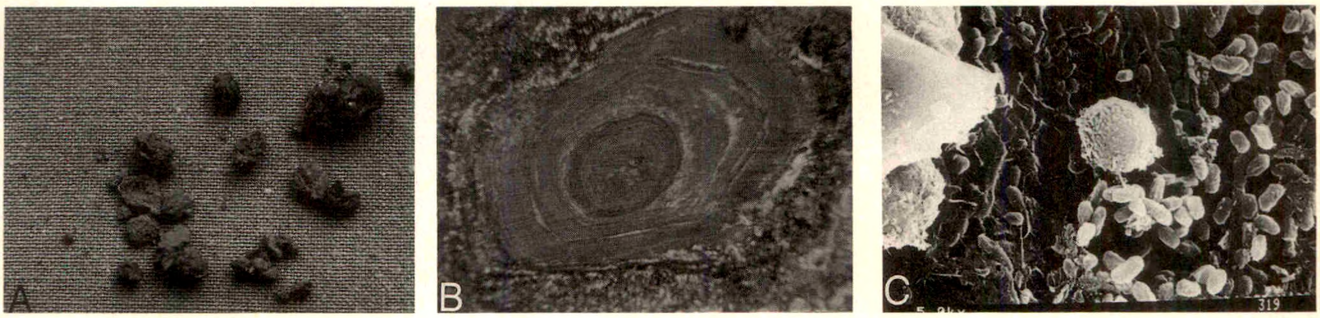
two patients had combination stones. Stones with a pigment coat but with a central nidus of a different composition from the periphery or stones entirely pigmented but found in the same site and concomitantly with cholesterol and mixed stones were not included in the pigment stone group. They were considered 'other stones' (n = 64), together with calcium salt stones and other rare types of stones (Table 1). A detailed analysis of patients with brown composite stones is given in Table 3.

Brown Stones

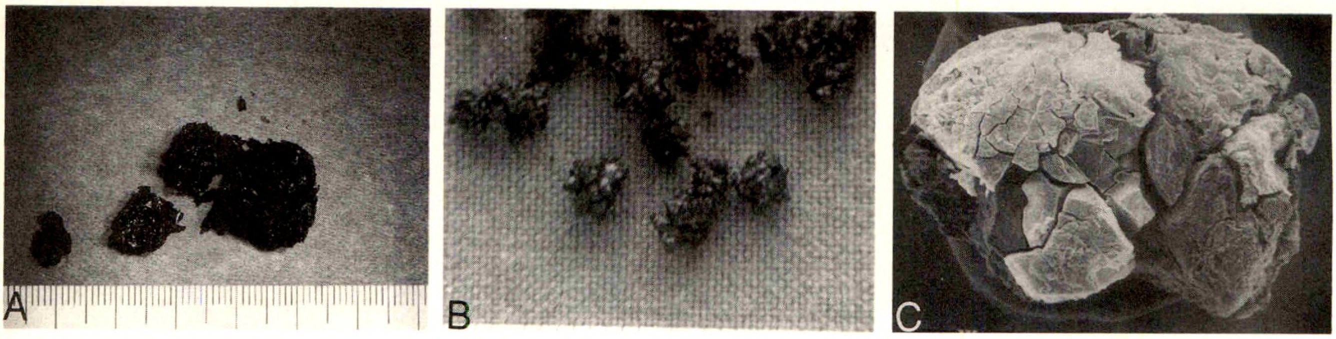
Brown stones were found as postcholecystectomy stones in 27 cases (Fig. 2A), in 21 cases in patients with no previous biliary surgery (Fig. 2B), and in 2 patients with spontaneous biliary enteric fistulas (Table 2). Twenty-two patients were men, 28 were women, with a mean age of 73.2 years (range, 50 to 87 years). Stones were found in 48 cases in the common duct, in 13 cases both in the common duct and in the gallbladder, and in 2 cases only in the gallbladder. Positive bile culture was found in 49 cases. Analysis of stone composition demonstrated the presence of calcium bilirubinate (51% ± 17%) and cholesterol (10.4% ± 6%), which was found in all brown stones. However the most specific compound of brown stones was calcium palmitate (23% ± 11%), a crystalline calcium salt that was almost never found in other types of gallstones. In particular calcium palmitate was found in brown stones in a concentration greater than 10% in 48 cases, both in the stone center and periphery (Fig. 5A). All of these stones were found in the common duct and all had positive bile culture.

Of the 27 patients with postcholecystectomy stones (Fig. 2A), 11 were men and 16 were women, with a mean age of 69.5 years (range, 50 to 76 years). Stones were single in 10 cases and multiple in 17 cases. Brown stones contained nonabsorbable suture material in five cases and phytobezoars in another five cases. Bile culture was always positive in a concentration greater than 10^5 CFU/mL. *E. coli* was found in all cases, alone in 11 cases, and in association with other bacteria (Proteus, Enterobacter, *Pseudomonas, Klebsiella*, Enterococcus) in the other cases. Bile pH was 6.9 ± 0.32 (range, 6.2 to 8.0). Mean lithogenic index (in 21 patients) was 1.44 ± 0.32 (range, 1.02 to 1.94).

Stone composition demonstrated, in all the patients, the presence of calcium bilirubinate, calcium palmitate, and cholesterol. In three patients with white material macroscopically evident both in the stone center and periphery, calcium carbonate also was found. X-ray diffractometry demonstrated in all three cases the presence of aragonite, which is the less frequent crystalline phase of



FIGS. 2A–C. (A) Recurrent common duct brown stones. They look like aggregates of brown mud. (B) Gallbladder brown stone of an 82-year-old woman. Note the alternate dark and tan layers. (C) Scanning electron microscopy of a fresh recurrent brown stone: bacteria are clearly evident in the stone center. Magnification, 5000×. Bile culture: *E. coli* 10^6 > CFU/mL.



FIGS. 3A–C. Black mud (A) and black microstones (B). Note the irregular surface with multiple spiculas. (C) Scanning electron microscopy of a black stone: typical amorphous aspect; no bacteria.

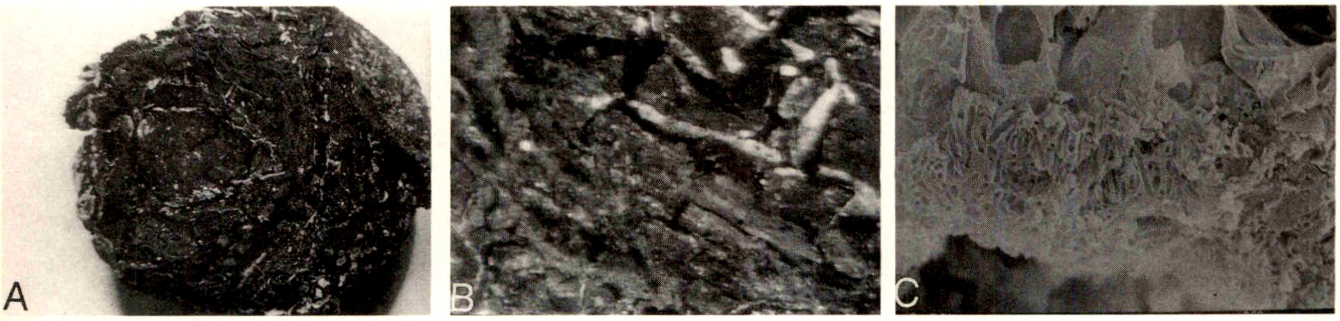
calcium carbonate in gallstones and which precipitates at lower pH.

All of these patients, in addition to cholecystectomy, had previous complementary surgical procedures on the bile tract. They were sphincterotomy in 19 cases, choledochoduodenostomy in 3 cases, hepaticojejunostomy in 1 case, and choledochotomy plus T-tube drainage in 4 cases.

The 21 noncholecystectomyzed patients with brown stones had stones in the common duct in 19 cases. Twelve of these patients had concomitant gallbladder brown stones (Fig. 2B). The last two patients had stones only in the gallbladder.

The 19 patients with common duct stones included 10 men and 9 women. Mean age was uniformly high: 80.36 years (range, 75 to 87 years). Age difference between patients with and without previous biliary surgery was highly significant ($p < 0.001$). Age difference also was significant between this group and the group with black pigment stones. Sex prevalence (10 men and 9 women) also was different from all other groups of patients with gallstones. Analysis of stone composition gave similar findings, as in cases of stones with previous cholecystectomy. Calcium palmitate always was present but usually it was found in smaller amounts (Fig. 5). Pigment material usually accounted for more than 50% of stone dry weight. Data from both x-ray diffractometry and infrared spectroscopy were extremely similar in both cases (Fig. 5). Bile culture was always positive and the same bacteria were found as in patients with postcholecystectomy brown stones. Mean lithogenic index (in four patients) was 1.56 ± 0.39. Mean pH of the common duct bile was 7.2 ± 0.50. Differences between lithogenic index and bile pH were not statistically different in the two groups ($p > 0.1$).

Brown stones were homogeneous in cross-section in both groups, with no evident difference between nucleus and periphery (Figs. 2A and B). In the same subject, gallbladder stones had the same composition as common duct stones. Mixed or composite stones, with a nucleus of different composition and origin from the periphery, were not included in this group. However it was noteworthy that (1) brown stones in the noncholecystectomyzed patients were usually larger in size and harder in density than postcholecystectomy stones, which often appeared as true aggregates of biliary mud (Figs. 2A and B); (2) a laminar structure, with eccentrically shaped rings in cross-section always was detectable in the former group (Fig. 2B), while it was almost never detectable in the latter with postcholecystectomy stones; and (3) the calcium palmitate content of brown gallbladder stones (16.0 ± 2.0; range,



FIGS. 4A–C. (A and B) A black and brown microstone, 4 mm in size, found in the commun duct of a patient with periampullary carcinoma. Stereomicroscopy clearly shows that it is not a combination stone, but black and brown material are tightly mixed both in the stone center and periphery. (C) SEM of a dry black and brown stone: note the typical bacterial casts, similar to those observed in brown stones. Magnification, 200×. Bile culture. *E. coli* 10^6 CFU/mL.

TABLE 2. *Brown Pigment Stones*

Stones	n	Age	Sex		Site		Positive Bile Culture	CP
			M	F	GB	CD		
After cholecystectomy	27	69.5	11	16	—	27	27	27
Noncholecystectomyzed patients CD	19	80.3	10	9	12	19	19	19
Noncholecystectomyzed patients GB	2	66	1	1	2	—	1	—
Spontaneous biliary enteric fistulas	2	68	1	1	1	2	2	2
Total brown stones	50	73.2	23	27	15	48	49	48
Black and brown gallstones	9	74.3	5	4	2	9	9	9
Total	59	73.4	28	31	17	57	58	57

GB, gallbladder; CD, common duct; CP, calcium palmitate.

5.5 to 35.0) was less than that of common duct stones in the former group and than that of postcholecystectomy stones ($p < 0.01$). In addition the calcium palmitate content of common duct stones was always greater than that of gallbladder stones in the same patient, even if the calcium palmitate content of the gallbladder stones of one patient could be greater than that of the common duct stone of another patient (Fig. 5A). Scanning electron microscopy of stones demonstrated the presence of calcified bacteria or bacterial casts in patients with recurrent common duct brown stones and in patients with brown stones without previous biliary surgery, while usually they were not found in cholesterol or black gallstones (Figs. 1C, 2C, 3C, 4C; Figs. 6A and B).

Spontaneous biliary enteric fistulas were found in 13 cases. Ten patients had a cholecystoduodenal and three had cholecystocolic fistulas. There were nine men and four women (sex prevalence completely different from all other groups of patients with gallstones). Mean age was 64.7 years (range, 46 to 80 years). Two patients with cholecystoduodenal fistula had no associated gallstones. Both had positive bile culture. Enterobacter was found in one case and Klebsiella in the other. Two patients (Table 2) had brown stones only. In one case, a 56-year-old man had a small brown stone in the gallbladder 3 months after a previous operation for gallstone ileus due to a large cholesterol stone. In the other case, an 80-year-old man had brown stones both in the gallbladder and in the common duct 1 year after a partial gastrectomy, complicated by duodenal leakage (and subsequent cholecystoduodenal fistula). In the other nine patients with spontaneous biliary enteric fistulas (mean age, 66.1 years) (Table 3), stones with a brown periphery or entirely pigmented were associated with cholesterol stones. In three cases stones were only in the gallbladder, in one case in the common duct, in the last five cases both in the gallbladder and in the common duct.

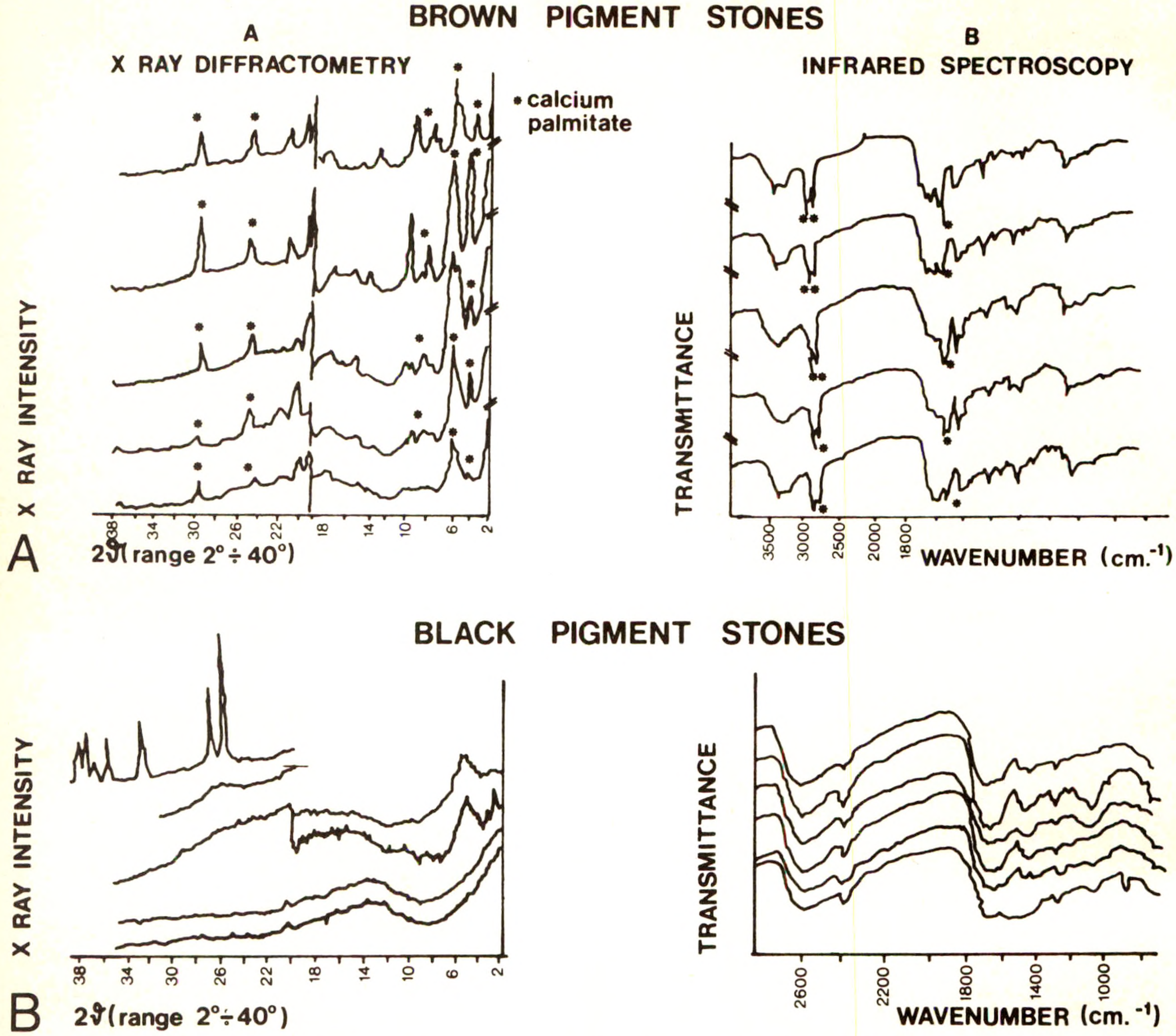
TABLE 3. *Composite Brown Stones*

Stones	n	Age	Sex		Site		Positive Bile Culture	CP
			M	F	GB	CD		
Spontaneous biliary enteric fistulas	9	66.1	8	1	8	6	8	8
Postcholecystectomy retained stones	6	50.6	3	3	—	6	6	6
Cholesterol GB stones and composite CD stones	9	63	3	6	7	7	4	3
Cholesterol stones and brown mud in GB	4	51	2	2	4	—	1	—
Cholesterol stones with black coat in GB and brown coat in CD	1	63	1	—	—	1	1	1
Total	29	65	17	12	19	20	20	18

GB, gallbladder; CD, common duct; CP, calcium palmitate.

Stones with a cholesterol nucleus and a brown periphery also were found in the present series, in six patients after cholecystectomy. They were classified as other stones in Table 1. These stones were probably retained stones that formed a pigment coat in the common duct. Bile culture was always positive. Calcium palmitate was always present in the brown coat (Table 3).

The last two patients with gallbladder brown stones (a 50-year-old man and an 82-year-old woman) had typical single brown stones (measuring 0.7 cm and 4 cm, respectively). The former patient, an alcoholic, had a history of pancreatitis and cholangitis and had multiple hepatic abscesses at operation but no common duct stones detectable by intraoperative cholangiography. The latter underwent surgery for acute cholecystitis. Bile culture was positive for Klebsiella in the first case and negative in the other (*i.e.*, less than 10^5 CFU/mL). Bile pH was 7.2. and 7.4, respectively. Analysis of stone composition demonstrated the presence of calcium bilirubinate and cholesterol. Calcium palmitate was not detectable in a diffractometrically evident amount (*i.e.*, more than 5% of stone dry weight), even if small white beads, mainly consisting of calcium

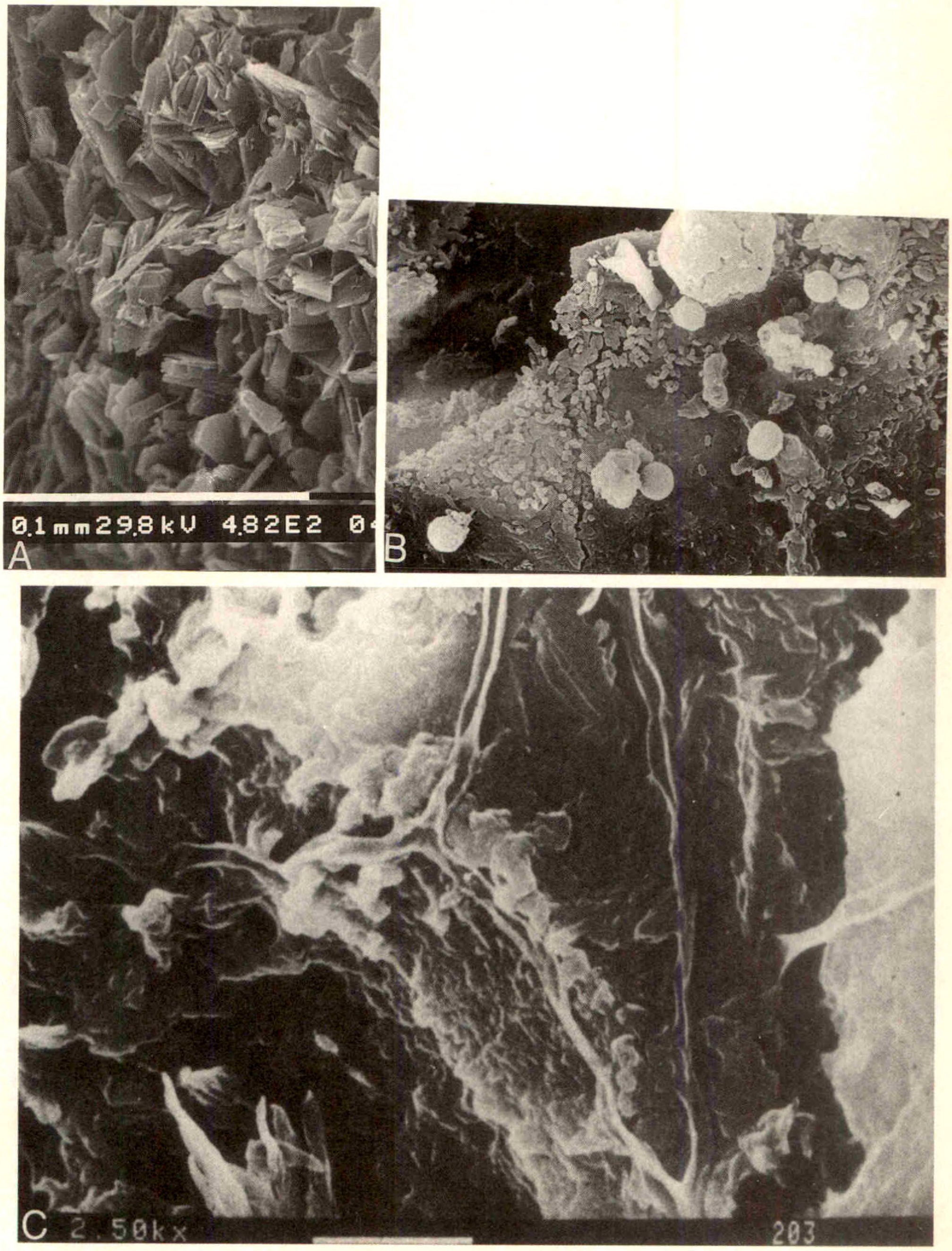


FIGS. 5A and B. (A) X-ray diffractometry of black stones and of brown pigment stones: five different patients with brown stones and six patients with black stones. Note the complete absence of spikes in amorphous black stones and the typical bands of calcium palmitate in brown stones. The first three diffractograms and IR spectra are of recurrent common duct stones. The last two are of brown stones in patients with no previous surgery. (B) Infrared spectroscopy: IR spectra of black stones are irregular, only slightly indented, with no evidence of spikes. Brown stones show more evident calcium bilirubinate bands and the typical bands of calcium palmitate.

palmitate, were macroscopically evident both in the center and in the periphery of the larger stone.

In 13 patients with no previous biliary surgery, brown stones were associated with cholesterol stones or contained a cholesterol nucleus in the common duct or in the gallbladder. In these patients bile culture was positive in only five cases while calcium palmitate was found in three cases (Table 3). Finally a patient who initially refused surgery underwent operation 4 months after the onset of jaundice and after suffering from multiple episodes of cholangitis. Gallstones were found in the gallbladder and in the common duct. They had a cholesterol nucleus in both sites. However gallbladder stones had a black periphery with multiple spiculas (containing bilirubinate and carbonate), while the three stones found in the common duct, which probably were responsible for jaundice, had a brown periphery containing calcium palmitate. Bile culture demonstrated the presence of *E. coli* and proteus sp. (Table 3).

Histologic examination of the gallbladder wall in patients with brown stones and gallbladder still *in situ* usually demonstrated the presence of chronic and acute inflammation, with diffuse erosion of the mucosa, loss of the epithelium, and microabscesses. The same findings also



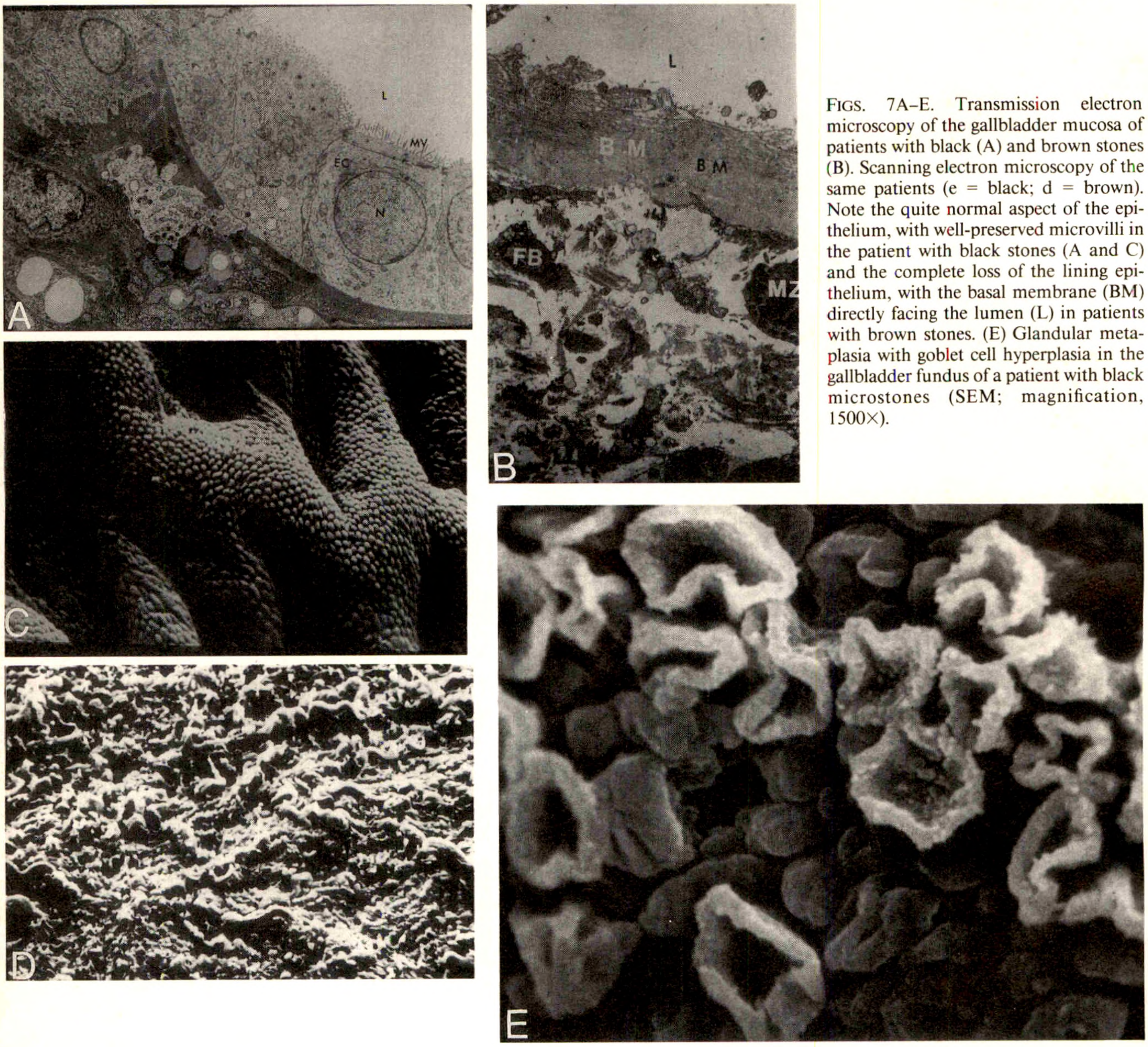
FIGS. 6A–C. (A) Cholesterol stone by SEM. Cholesterol crystals, no bacteria. Magnification, 480×. (B) Brown pigment stones by SEM. Note the typical presence of calcified bacteria both in the stone center and surface. (C) Mucus filaments both on the surface and in the center of a black pigment stone (SEM; magnification, 2500×).

were observed in common duct specimens obtained in patients who underwent biliary enteric anastomoses for postcholecystectomy brown stones. Both scanning and transmission electron microscopy showed diffuse alterations of the common duct mucosa (Figs. 7B and D).

Black Stones

Black pigment stones were found in 22 men and 29 women. Mean age was 58.8 ± 12.5 years (range, 20 to 89 years). Stone size and site and bile culture are reported in Table 4 (Figs. 3A–C). Analysis of stone composition (Fig. 5B) demonstrated the presence of pigment material (61.8% ± 11.6%), calcium carbonate (6.5% ± 6.0%), calcium phosphate (3.0% ± 1.5%), and little cholesterol (7.5% ± 4.7%). In particular cholesterol was found in only 23 patients, while it was always found in brown pigment stones. Calcium palmitate was never found in diffractometrically evident amounts (*i.e.*, more than 5% of stone dry weight) in black pigment gallstones (Fig. 5B).

Associated clinical findings were cirrhosis in 11 cases, alcoholism in 5 cases, long-lasting use of drugs in 8 cases,



FIGS. 7A–E. Transmission electron microscopy of the gallbladder mucosa of patients with black (A) and brown stones (B). Scanning electron microscopy of the same patients (e = black; d = brown). Note the quite normal aspect of the epithelium, with well-preserved microvilli in the patient with black stones (A and C) and the complete loss of the lining epithelium, with the basal membrane (BM) directly facing the lumen (L) in patients with brown stones. (E) Glandular metaplasia with goblet cell hyperplasia in the gallbladder fundus of a patient with black microstones (SEM; magnification, 1500×).

and malignancies in 6 cases. It is noteworthy that patients with clinically evident hemolytic diseases were found in only 3 cases, aged 27, 47, and 49 years, respectively, despite the fact that in Italy thalassemia and sickle cell anemia have a high incidence in many areas.

Histologic examination of the gallbladder wall demonstrated in most cases the presence of hyperplastic cholecystosis with little or no signs of chronic inflammation (Figs. 7A and C). Acute inflammation was found in only 15 cases. Mucous cell metaplasia was found in 40% of black stones, which were analyzed by scanning electron microscopy (Fig. 7E). Black stones frequently were associated with mucus hyperproduction. This phenomenon could be detected both macroscopically (black microstones usually are embedded in a tight mucus network) and microscopically, either in gallbladder or in stone specimens. In particular scanning electron microscopy showed the presence of long mucus microfilaments, tightly adherent to black gallstones (Fig. 6C).

Brown and black pigment stones were found in nine cases: five men and four women (mean age, 74.3 years) (Table 5). This finding also was reported by others.[8–10] Most of them (seven of nine) were found in patients with periampullary carcinoma. They usually appeared as small conglomerates that were crushed easily with forceps or fingers and had alternate irregular black and brown concentric layers in cross-section (Figs. 4A–C). Analysis of stone composition showed the presence of calcium pal-

TABLE 4. *Black Pigment Gallstones (n = 51)*

	Sex		Stones			Bile				
			Site							
Age	M	F	GB	CD	Size	pH	L.I. (n = 18)	Positive Culture	Clinical Findings	Associate Pathologic Findings
58.8 ± 12.5 + − 12, 52	22	29	50	11	6 single (5–10 mm) 2 double (10 m) 5 black mud 5 multiple (3-6 mm) 33 multiple (3 mm)	7.27 + − 0.47	1 + − 0.28	10	11 Cirrhosis 5 Alcoholism 8 Drugs 6 Cancer 5 Gastric surgery 2 Colon surgery 3 Hepatitis HBS + 3 Recent Weight Loss 5 Nonspecific	15 Pancreatitis 5 Hyperplastic cholecystosis with adenomyomatosis 2 Empyema 2 Hemorragic cholecystitis 1 Septicemia 1 Liver abscesses

mitate, which is the typical calcium crystalline compound of brown stones.

Bile Infection

Bile infection (*i.e.*, a bacterial concentration in the bile greater than 10^5 CFU/mL) was found in 229 of the 960 patients (23.8%). Bile was infected in 49 of 364 patients with ovoidal cholesterol stones (13.5%), 70 of 350 patients with faceted mixed cholesterol stones (20%), 49 of 50 patients with brown pigment stones (98%), 10 of 51 patients with black pigment stones (19, 6%), 9 patients with black and brown pigment stones (100%), 29 patients with combination stones (40%), and 13 patients with 'other stones' (20.3%) (Table 1). *E. coli*, alone or in association with other bacteria, was found in 153 of the 229 positive bile cultures (66.8%). Seven hundred thirty-one patients had negative cultures. Fifty-eight patients with homogeneous brown stones (49 brown and 9 black and brown) had both bile infection and calcium palmitate in gallstones. Eighteen additional patients with composite stones, including brown material, also had both bile infection and calcium palmitate (Table 3). On the contrary there were (1) two patients with bile infection and calcium palmitate in nonbrown stones; and (2) two patients with brown stones and calcium palmitate, not associated with evident bile infection, and six patients with brown stones not containing calcium palmitate and not associated with evident bile infection (*i.e.*, less than 10^5CFU/mL). All of these six patients had brown stones in the gallbladder, while common duct brown stones always contained calcium palmitate and always were associated with bile infection. In particular *E. coli* always was present.

Among the 153 patients with bile infection by *E. coli*, brown stones were associated in 81 cases (52.9%) and calcium palmitate was found in 79 (51.6%). In one of the two patients with brown pigment gallbladder stones not containing calcium palmitate and in the two patients with spontaneous biliary enteric fistulas with no associated stones, bile culture was positive but *E. coli* was absent. Klebsiella was cultured in two cases and Enterobacter in the last case. Sixty-three patients had stone culture. Fifty-five patients had scanning electron microscopy (SEM) of stones. In all of the patients with positive stone culture or with bacteria demonstrable in the center of stones by SEM, bile culture also was positive. In the present series, no patient was found with bacteria demonstrable in the stone center by SEM, both directly and indirectly (bacterial casts), who had negative bile culture (Figs. 1C, 2C, 3C, 4C; Figs. 6A and B).

In black stones bile culture was associated in 19.6% of cases, mostly in stones that were found concomitantly in the gallbladder and common duct or in patients with previous pancreatitis. In 10 patients with black stones, who were analyzed by SEM, bacteria were never found (Figs. 3 and 6C), while they were always found in the four (of nine) patients with black and brown stones in whom SEM was performed (Fig. 4C).

Discussion

In a surgical series of consecutive patients from a Western country such as Italy, pigment stones were found as unique stones in 11.45% of cases. Pigment stones were brown in 45.4% and black in 46.3% of cases. In nine additional patients (8.2% of pigment stones, 0.9% of all gallstones), concomitant black and brown stones were found. In addition pigment material was found in 53 other patients (29 with brown pigment and 24 with black pigment), with combination stones or stones classified as 'other stones' (5.52 of all gallstones). In these cases pigment material usually formed the peripheral coat of stones with a different nucleus (usually cholesterol).

Brown stones were found mostly in the common duct (48 of 50 cases), almost always (48 of 50) contained calcium palmitate as typical compound,[20] and were associated with bile infection (*i.e.*, a bacterial concentration greater than 10^5CFU/mL) in 49 of 50 patients. In particular common duct brown stones always were associated with bile infection, while brown stones from the gallbladder sometimes were not associated with bile infection (1 of 19) and did not contain calcium palmitate (2 of 19). These observations correlate with previous findings reported by Tabata and Nakayama.[7] In addition present findings suggest that not only the mere positivity of bile culture but also the site of stones (gallbladder or common duct: see also data in patients with composite stones or with biliary digestive fistulas) and the type of bacteria (*E. coli*) are possible determinants of the brown pigment and calcium palmitate concentrations in the stones. On the other hand, black stones usually were found in the gallbladder, never contained evident amounts of calcium palmitate, and were associated with bile infection in only 19.6% of cases.

Other associated findings also were very different. Brown stones usually were found as postcholecystectomy stones (n = 27), in older patients with bile stasis (n = 19), or in patients with spontaneous biliary enteric fistulas (n = 13) (Table 2). In most of these patients bile stasis was evident, due to a stricture of a previous sphincterotomy or of a biliary enteric anastomosis or to age-dependent degenerative alterations of the sphincter of Oddi or of the lower portion of the common duct.[4] Black stones, on the other hand, were associated with hemolysis or with a previous or current liver damage (cirrhosis, hepatitis, long-term use of psycodrugs, and so on) (Table 4). Mean age of patients was also different, particularly in patients with no previous biliary surgery (80.36 in brown stones, 58.8 in black stones) ($p < 0.001$). In particular black stones were found in patients as young as 27 years, even in the absence of evident hemolysis, while brown stones were never found as unique stones in patients younger than 50 years.

Histologic examination of the biliary mucosa also gave different results in the two groups. Diffuse erosion of the gallbladder and common duct mucosa, loss of the lining epithelium, and parietal microabscesses were found in patients with brown stones (Figs. 7B and D). On the other hand, hyperplastic cholecystosis, associated in 40% of cases with mucous cell metaplasia, was found in patients with black stones. A quite normal mucosa, with no or poor signs of chronic inflammation, was another common finding in the black stone group (Figs. 7A and C).

Because we have analyzed constantly stones in relationship to bile and parietal wall (gallbladder and bile duct mucosa), we can state that not only composition of stones but also parietal and environmental characteristics are very different in patients with black and brown stones. Therefore present findings confirm our previous data published in 1983 to 1986[3–5] and lend support to the suggestions by Malet et al.[20] and Kaufman et al.[9] that differences in structure between black and brown stones reflect fundamentally different mechanisms of stone formation.[21] On the other hand, our data do not correlate, at least in part, with the conclusions of Stewart et al.[8] and Smith et al.,[12] who do not distinguish between brown and black stones because of the frequent finding of concomitant black and brown stones. In addition they classify together as 'infectious stones' (1) brown pigment stones that contain bacteria (and calcium palmitate) both in the center and in the periphery; (2) combination or composite stones that have a brown periphery, usually associated with infection, but not always containing calcium palmitate (and that had at least two different mechanisms in their pathogenesis, the former responsible for the cholesterol nucleus and the latter for the pigment periphery); (3) all gallstones with bacteria found on the stone surface.

In our series, in addition to 50 patients with homogeneous brown stones and 51 with black stones, we also found 9 patients with concomitant black and brown stones. These stones were never combination or composite stones with a black nucleus and a brown coat or vice

TABLE 5. *Black and Brown Stones*

n	Age (years)	Sex	Site GB	 CD	Bile Culture	CP	Associated Findings
1	67	M		+	+	+	Periampullary carcinoma
2	81	F	+	+	+	+	Multiple liver abscesses
3	69	M		+	+	+	Cirrhosis, ascitis, carcinoma of the colon
4	89	F		+	+	+	Pancreatic carcinoma
5	77	M	+	+	+	+	Periampullary carcinoma
6	81	M		+	+	+	Periampullary carcinoma
7	66	M		+	+	+	Periampullary carcinoma
8	65	F		+	+	+	Periampullary carcinoma
9	74	M		+	+	+	Periampullary caricinoma
9 (Total)	74.3	6M − 3F	2 GB	9 CD	9+	9	6 periampullary carcinoma 1 pancreatic, 1 colon carcinoma 1 multiple liver abscesses

GB, gallbladder; CD, common duct; CP, calcium palmitate.

versa, but they always had typical brown and black material both in the center and in the periphery (Figs. 4A to C). They were found mostly in the common duct, were always associated with bile infection, and always contained calcium palmitate. Therefore they can be considered to share the same pathogenesis as brown stones. Excluding this small group of nine patients, all other pigment stones can be distinguished as brown and black, which greatly differ not only in composition, structure, and pathogenesis but also in clinical behavior and thus they require a different treatment.

In fact infectious brown stones are more likely to cause symptoms and require surgery than other types of stones.[12] In our study patients with brown stones presented with acute cholangitis in 60% of cases, while patients with noninfectious stones had associate cholangitis in only 23% of common duct stones. These figures correlate with those previously reported by Smith et al.[12] (52% in infectious stones, 18% in noninfectious stones). However it must be stressed that not all brown stones produce symptoms because typical cholangitis with fever and chills only occurs when sudden hypertension in the bile ducts is also associated, thus determining the passage of bacteria from the biliary tract into the blood stream. In a long-term follow-up study of patients with sphincterotomy or sphincteroplasty, we found that two patients with recurrent stones (including one patient with a 4-cm large stone, resembling in shape a true cast of the confluence between the main hepatic ducts and the common duct) were asymptomatic 5 years after sphincterotomy.

On the other hand, we recently documented that black pigment stones frequently are associated, because of their size (microlithiasis) (Table 5), density (high content in calcium carbonate and phosphate), and structure (presence of multiple spiculas on stone surface) (Fig. 3B) with pancreatitis, probably due to the easier obstruction of the ampulla of Vater by such stones.[22] However, in almost 50% of these cases (7 of 15), black stones were found only in the gallbladder but not in the common duct at the time of cholecystectomy. Therefore, because black stones never reform after cholecystectomy,[2] simple cholecystectomy could have been curative not only in the 35 patients without pancreatitis but also in one half of the patients with associated pancreatitis.

In addition we suggest that both cholesterol and black pigment stones form with a mechanism that is completely different from the stasis–infection mechanism. We also can provide evidence that the two mechanisms (metabolic and stasis–infection) are mutually exclusive of each other and that, particularly in the common duct, no stone other than brown pigment can reform after the initial formation of infectious brown stones. In our prospective study we documented that brown stones can form after cholecystectomy in patients with previous cholesterol or black stones,[5] but the opposite was never observed. In particular, in a 67-year-old woman who had cholecystectomy and sphincterotomy for a single ovoidal cholesterol stone (saved by the patient) in 1968, brown stones were found at the first reoperation (repeated sphincterotomy in 1971) and always were found at the second operation (choledochoduodenostomy in 1974), third reoperation (sphincteroplasty in 1984), and fourth reoperation (hepaticojejunostomy in 1987).

Therefore, even if common duct parietal alterations due to bile stasis (Figs. 7B and D) were shown to be reversible after removal of the stenosis (Lygidakis, oral personal communication, 1988), in our opinion, when the vicious circle of infection–stasis–infection, which is crucial for brown stone formation, has begun and brown stones have formed, they will recur almost invariably, regardless of the treatment performed. Drainage procedures (large biliary enteric anastomoses, not sphincterotomy, should be used liberally in patients with brown pigment stones. They cannot prevent permanently brown stone reformation, but if they can assure good biliary clearing for a long period, they could minimize symptoms, even if aggregates of brown mud (*i.e.*, brown stones) continue to form in the ducts. On the other hand, drainage procedures[12] (sphincterotomy, cholechoduodenostomy) are not only unnecessary but also harmful in patient with 'pure' black pigment gallstones, which never reform after cholecystectomy.[2]

We documented that recurrent common duct brown stones form mostly in patients with a previous sphincterotomy or sphincteroplasty for cholesterol, mixed, or black pigment stones. It can be hypothesized that sphincteric damage and bypass allow bile and duodenal juice to mix in the common duct. If duodenal content is sterile, bile is not infected and brown stones do not form. When duodenal content becomes infected with age and associated intestinal motor disorders or gastric pathology, bile is also contaminated and, if bile stasis is concomitant, due to a stricture of the sphincterotomy, brown stones can form.

In conclusion (1) bacteria actually constitute a substantial portion of brown stones and are primarily responsible for the formation of brown stones, which account for the majority of pigment stones also in Western countries as well as in the Orient[3–6] (53.5% of pigment stones, 6.1% of all gallstones in the present series). On the other hand, bacteria are not involved in the formation of cholesterol stones[10–12] and in that of the great majority of black stones,[12] which have a pathogenesis different from stasis–infection; (2) a sharp distinction between black and brown stones is not only useful for a better knowledge of the pathogenesis of the two main types of pigment gallstones but is also crucial for clinical and therapeutic purposes, including the proper selection of the therapeutic options on the basis of stone type and etiology.

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Early Gastric Cancer

Twenty-eight–Year Experience

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A retrospective study of early gastric cancer (60 patients) was performed to evaluate its diagnosis and treatment. Ninety-five per cent of patients presented with nonspecific gastrointestinal symptoms and 53.3% had been treated for presumed benign disease for up to 48 months before diagnosis. Fiberoptic endoscopy detected these lesions more accurately than radiologic examination. The disease-free 5-year survival rate after resection was 76.4%. Survival showed no significant correlation with sex, tumor site, macroscopic appearance, extent of gastric resection, or histopathologic type. Tumors larger than 1.5 cm in diameter, invasion of submucosa, or lymph node metastasis resulted in significantly lower survival rates. Three of eight patients with nodal metastasis survived 5 or more years, including one who had second-echelon deposits. A high index of suspicion may permit more frequent detection. Extended lymphadenectomy (R2) is recommended to achieve the highest possible cure rate.

GASTRIC CARCINOMA IS still one of the ten major causes of death due to cancer in the United States, even though its incidence decreased during the last three decades. Substantial interest has arisen in recent years in the diagnosis and management of early gastric cancer because very high cure rates can be achieved in this as compared with advanced stages of this disease.[1–4] In the early 1960s, the Japanese Gastroenterological Endoscopy Society defined early gastric cancer as carcinoma limited to the gastric mucosa and submucosa, regardless of the presence or absence of lymph node metastases.[4] The Japanese Research Society for Gastric Cancer provided a macroscopic classification of early gastric cancer in 1981.[5] Three types were described: type I, protruded lesions; type II, superficial lesions that may be flat (IIa), minimally elevated (IIb), or minimally depressed (IIc); and type III, excavated or depressed lesions.

In a recent report from the Tokyo Women's Medical College of 1019 patients with early gastric cancer resected for cure between 1965 and 1982, 5-, 10-, and 15-year survival rates of 95%, 90%, and 85%, respectively, were observed.[6] The improvement in survival is attributed to early diagnosis by the use of mass screening programs, increasingly sophisticated equipment such as the panendoscope and enlargement fiberscope, and advanced techniques including dye-spraying endoscopy and spectrophotometric color analysis of gastric mucosa. With these methods the incidence of gastric cancer diagnosed at this early stage has increased in Japan from 5% to more than 30% during the past 15 years, with 2400 cases reported in 1980.[7]

Although the numbers are less impressive, reports of early gastric cancer have appeared in the western literature.[8–11] These reports have corroborated the Japanese findings of a high cure rate of gastric cancer when diagnosed and treated before infiltration of the muscularis propria. Vigorous efforts therefore have been initiated toward the early detection of these tumors worldwide. In the United States approximately 23,000 cases of gastric cancer are reported annually but the incidence of early gastric cancer detection is only 3% to 6%, or approximately 1400 cases per year.[12] Mass screening of this population is difficult to justify on economic grounds but evidence suggests that greater clinical suspicion and meticulous repeated diagnostic evaluation, especially by endoscopic examination of selected patients, may increase the rate of detection of these early lesions.

The purpose of the present study was to review the experience of patients treated for early gastric cancer at our center to determine whether there is a specific pattern of clinical, laboratory, radiographic, or endoscopic features that could distinguish them from patients with benign gastric disease. Accuracy of our diagnostic methods, rea-

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sons for diagnostic delay, and the outcome of treatment also were analyzed.

Methods

Patients with early gastric cancer were identified from two databases of gastric cancer at the Memorial Sloan-Kettering Cancer Center: one was a retrospective collection of curatively treated gastric carcinomas (1960 to 1984) and the other was a prospectively maintained database started in 1985. Sixty patients were found to meet the histologic criteria for early gastric cancer. These patients' medical records were reviewed to ascertain the type and duration of symptoms, clinical, laboratory, radiographic, and endoscopic findings, type of gastric resection, tumor size, location, histologic differentiation, depth of gastric wall invasion, lymph node status, and follow-up information, including recurrence and survival. The tumors were also categorized by their macroscopic appearance according to the Japanese Research Society for Gastric Cancer.[5] Survival distributions were computed using the method of Kaplan and Meier[13] and univariate analyses of survival comparing patient subgroups were performed using the log rank statistic.

Results

Of the 60 patients who had early gastric cancer during the 28-year period of the study, 10 were treated during the first half and 50 during the second half of this period. There were 35 men and 25 women; the male to female ratio was 1.4:1. They consisted of 51 whites, 5 Asians, 2 blacks, 1 Hispanic, and 1 Indian. Seventeen of the patients were born abroad and immigrated to the United States; the length of residence in the United States ranged from 21 to 62 years. The mean age at diagnosis was 62 years, with a range of 44 to 89 years.

Associated Diseases

Gastric cancer was a second primary malignant tumor diagnosed in 10 of the 60 patients, occurring 2 to 20 years after treatment of the first primary tumor. The sites of the first malignant tumor included the rectum in three patients, uterine cervix in two patients, and, in one patient each, the lung, breast, skin, larynx, and renal pelvis. None of these patients had evidence of their first malignancy at the time the diagnosis of early gastric carcinoma was made.

Fifteen patients (25%) had pre-existing conditions that may be implicated in the development of gastric carcinoma; the conditions were documented 2 to 27 years before the diagnosis of gastric cancer was made. Twelve patients had long-standing peptic ulcer disease; two of these patients underwent subtotal gastrectomy 17 years earlier. In three patients, two of whom had Barrett's esophagus and one had pernicious anemia, gastric cancer was detected by yearly surveillance studies.

Presenting Features

Fifty-seven of the sixty patients (95%) underwent diagnostic studies for upper gastrointestinal symptoms. Epigastric pain and dyspepsia were the most common complaints. Weight loss in 13 patients ranged from 6 to 23 kg during a 2- to 10-month period. Forty-two per cent of the patients sought medical attention within 2 months of onset of their symptoms. The remaining 58% endured their symptoms from 3 to 72 months before seeking medical consultation. Seventy-two per cent of patients had no physical findings referable to their gastric lesions. The most frequent physical finding was epigastric tenderness, present in 10% of the patients. Anemia was the most common laboratory abnormality; it was found in 21.6% of the patients.

Methods of Diagnosis

The diagnostic methods and the sequence in which they were used differed according to the time period in which the patient was treated and whether the patient first consulted a gastroenterologist or a physician of some other specialty. Fiberoptic gastroscopy was not commonly performed in the 1960 to 1970 period.

A diagnosis of cancer was obtained in all 12 patients who underwent endoscopy as their first diagnostic procedure. An average of four to six biopsies were taken to obtain the diagnosis. A computed tomogram (CT) was obtained as the first diagnostic procedure in one patient. Although thickened rugal folds were reported on CT, the definitive diagnosis of cancer was obtained later by endoscopy in this patient.

An upper gastrointestinal barium examination was the first study performed in 47 patients. Double-contrast examination with thin barium was not used routinely, except during the last 10 years. Malignancy was diagnosed in eight (17%) of these studies. Of the remaining 39 studies, 28 (59.6%) were reported as benign disease and 11 (23.4%) were equivocal. Six patients with reported benign disease underwent repeat radiographic examinations for persistent symptoms 2 to 12 months after their initial procedure; these radiographs were likewise considered to be consistent with benign ulcer disease. Endoscopy was performed subsequently on 37 of these 39 patients. A diagnosis of cancer was obtained by biopsy or cytology in 30 patients (81.1%), and of gastritis or peptic ulcer disease in seven patients. Repeat endoscopy was performed on these seven patients at 2- to 12-month intervals, resulting in the diagnosis of cancer in five. One of the seven patients underwent three endoscopic procedures during a period of 6 months, and another had six endoscopic procedures during a period of 18 months, before the definitive diagnosis was obtained. The remaining 2 of the 39 patients were brought to the operating room with presumed peptic ulcer disease, without benefit of preoperative endoscopy.

In total 32 of the 60 patients (53.3%) were diagnosed erroneously as having benign ulcer disease and/or gastritis and were treated with antacids and H2-receptor antagonists at the time of their initial presentation. The diagnostic delay ranged from 2 to 48 months (mean, 14.3 months) in these patients. Twenty-nine of these patients were treated for presumed benign disease on the basis of their radiographic findings. Endoscopic procedures subsequently were performed in this group of patients only when their symptoms proved refractory to medical therapy. Two of the seven patients who required multiple endoscopic procedures actually exhibited healing of the ulcer with improved symptoms at the time of repeat evaluation.

Surgical Treatment

The surgical procedure performed was based on the location and extent of the lesion in all instances. Distal subtotal gastrectomy was performed in 42 patients, esophagogastrectomy in 8 patients, proximal subtotal gastrectomy in 4 patients, total gastrectomy in 4 patients, and wedge excision of polyps in 2 patients. The latter procedure was performed before the popular use of fiberoptic endoscopy in two patients who had small gastric polyps visualized by upper gastrointestinal barium examination. Concomitant procedures included 8 splenectomies, 4 cholecystectomies, and 1 distal pancreatectomy. Six of the splenectomies and the pancreatectomy were performed as *en bloc* resections for tumors close to these organs. Two splenectomies were performed as a result of intraoperative injury. All four patients who underwent cholecystectomy had symptomatic biliary disease and preoperative evidence of cholelithiasis.

The extent of the lymphadenectomy performed reflected the opinion and judgment of the surgeon and varied considerably during the 28-year period of the study. Lymphadenectomy was classified as R1 if dissection included only the first echelon or immediately adjacent nodes, R2 if the second echelon of draining nodes was included, such as those along the left gastric, celiac, and common hepatic artery. Review of the operative reports indicated that two patients showed gross nodal metastases, which prompted the performance of wide lymphadenectomy. An R1 lymphadenectomy was performed in 40 patients and an R2 lymphadenectomy in 18; no lymph node dissection was performed in the two patients who underwent wedge polypectomy.

Fourteen complications occurred in 13 patients: pneumonia in 3, myocardial infarction in 2, anastomotic leak in 2, wound disruption in 2, wound infection in 2, small bowel obstruction in 1, and intra-abdominal abscess in 1. These complications resolved with medical treatment; no surgical intervention was required except in one patient who underwent operative repair of wound disruption. The anastomotic leaks were treated conservatively with bowel rest and parenteral nutrition. The intra-abdominal abscess was drained percutaneously with CT guidance.

Pathology

All tumors were adenocarcinomas and ranged in size from microscopic foci to 7 cm in diameter. Thirty arose in stomachs with a background of coexisting pathologic changes: chronic ulcer in 18, chronic gastritis in 7, intestinal metaplasia in 4, and mucosal atrophy in 1. Thirty-nine (65%) of the tumors were intramucosal; 21 (35%) extended into the submucosa. By macroscopic classification, there were 16 (26.7%) type I, 12 (20%) type II, and 32 (53.3%) type III lesions.

The type I protruded lesions were intramucosal in 12 (75%) and penetrated the submucosa in four patients (25%). The 12 type II superficial lesions were equally divided between the intramucosal and submucosal categories. Twenty-one (65.6%) of the type III excavated lesions were intramucosal and 11 (34.3%) invaded the submucosa.

The type II superficial lesions were generally smaller in size than either the type I protruded or type III excavated lesions; the mean diameters were 1.9, 2.4, and 2.5 cm, respectively. Twenty-seven (45%) cancers were located in the body of the stomach, 22 (36.7%) in the pyloric antrum, eight (13.3%) at the cardioesophageal junction, and three (5%) in the fundus. Protruded and excavated lesions were found more commonly in the antrum and body while the superficial lesions were located mainly in the body of the stomach. Most of the lesions were either grade 1 well differentiated (58.4%) or grade 2 moderately differentiated (33.3%) tumors with an even distribution among the three macroscopic types of cancer. Fifty-two (86.7%) of the tumors were of the intestinal type and eight (13.3%) of the diffuse type based on the histopathologic classification of Lauren.[14]

All surgical margins were microscopically negative. Metastatic deposits in lymph nodes were histopathologically confirmed in 8 (13.3%) of the 60 patients (Table 1). In five of these patients the deposit consisted only of a microscopic focus (less than 1 mm in diameter). Macroscopic replacement of lymph nodes was found in three patients, including one who had both microscopic and macroscopic deposits. Six of the eight patients had metastatic involvement of the first-echelon (N1) lymph nodes only; included in this group were all three patients with macroscopic deposits. Two of the patients had metastases in second-echelon (N2) lymph nodes; these were micro-

TABLE 1. *Early Gastric Cancer with Lymph Node Metastasis, Pathologic Features, Treatment, and Outcome*

Lymph Node Stage	Macroscopic Type	Depth of Invasion	Size (cm)	Lymphadenectomy	Outcome
N1	III	Mucosa	4.0	R2	NED 105 m
N1	I	Mucosa	7.0	R1	DOD 10 m
N1	III	Mucosa and submucosa	1.8	R1	DOD 45 m
N1	III	Mucosa and submucosa	4.8	R1	NED 77 m
N1	IIa	Mucosa and submucosa	2.0	R1	DOD 21 m
N2	III	Mucosa	1.4	R2	NED 60 m
N2	IIa	Mucosa and submucosa	1.8	R2	DOD 11 m
N2	III	Mucosa and submucosa	7.0	R2	DOD 12 m

DOD, dead of gastric cancer disease; m, months; NED, no evidence of disease.

N1, metastasis in lymph nodes within 3 cm of the tumor; N2, metastasis in lymph nodes farther than 3 cm from the tumor, such as those along the celiac, common hepatic, or splenic arteries.

R1 and R2 refer to lymphadenectomy with removal of the first or the first plus the second echelons of regional lymph nodes.

scopic deposits in the celiac node of a patient with a lesser curvature lesion and in a mediastinal paraesophageal node of a patient with a tumor in the cardioesophageal junction.

Five of the eight patients with nodal metastases had excavated lesions, two had superficial lesions, and one had a protruded lesion (Table 1). Three of the eight lesions were intramucosal; five invaded the submucosa. Five of the eight tumors were of the intestinal variety: one of protruded type, one superficial type, and three excavated type. Three were of the diffuse variety: two of excavated type and one superficial type.

Adjuvant Therapy

Only one patient, who had microscopic evidence of metastatic disease in the first-echelon (N1) lymph nodes, received adjuvant postoperative chemotherapy. This patient developed lung metastases 45 months after surgery and subsequently died of his disease.

Recurrence

Ten of the sixty patients (16.7%) developed either local or systemic recurrence of disease at a mean interval of 26 months after surgery. One half of these patients had lymph node metastases at the time of surgery. Eight of the ten patients who recurred had tumors that invaded the submucosa. With regard to histologic grade, three of the ten patients had well-differentiated (grade 1) tumors, six had moderately well-differentiated (grade 2) tumors, and one had a poorly differentiated (grade 3) tumor. The mean survival of this group was 2.7 months after detection of recurrence.

Survival

None of the patients died within 30 days of the operation or at any time during their postsurgical hospital stay. Survival data was available in all 60 patients. Follow-up times ranged from 11 to 270 months (mean, 57 months) from the date of resection. The Kaplan–Meier estimates of 5- and 10-year disease-free survival rates were both 76.4% (Fig. 1). Ten patients (16.7%) died of recurrent gastric cancer; nine died of other causes. The remaining 41 patients are alive without evidence of tumor recurrence.

Comparison analysis of the survival distributions showed that there was no significant difference in the disease-free survival of patients based on sex, the location of the cancer within the stomach, macroscopic appearance, extent of gastric resection, scope of regional lymphadenectomy, or the Lauren histopathologic type. There was, however, a significant difference in survival according to tumor size, depth of invasion, and the presence or absence of lymph node metastases.

Figure 2 shows the difference in the survival distribution according to the size of the tumor ($p < 0.05$). The 5-year disease-free survival for the 18 patients with tumors measuring less than 1.5 cm was 100% compared with 67.5% for the 42 patients with tumors larger than 1.5 cm. Only one of eighteen patients with a tumor less than 1.5 cm had lymph node metastases at the time of surgery. This patient, who had a type III excavated tumor with second-echelon (N2) nodal involvement, is without evidence of disease 60 months after resection with R2 lymphadenectomy. Fifteen of eighteen patients with small tumors had intestinal type and three had diffuse type lesions.

The difference in survival distribution according to the depth of invasion ($p < 0.0005$) is shown in Figure 3. Intramucosal lesions in 39 patients resulted in a 92.6% 5-year disease-free survival rate, in contrast to 48.8% for tumors that invaded the submucosa in 21 patients.

The presence or absence of lymph node metastasis had a significant influence on disease-free survival ($p < 0.00005$), as shown in Figure 4. Only three of the eight patients with positive lymph nodes, as compared with 45 of 52 (87%) for patients with negative lymph nodes, survived free of disease after 5 years. The three survivors

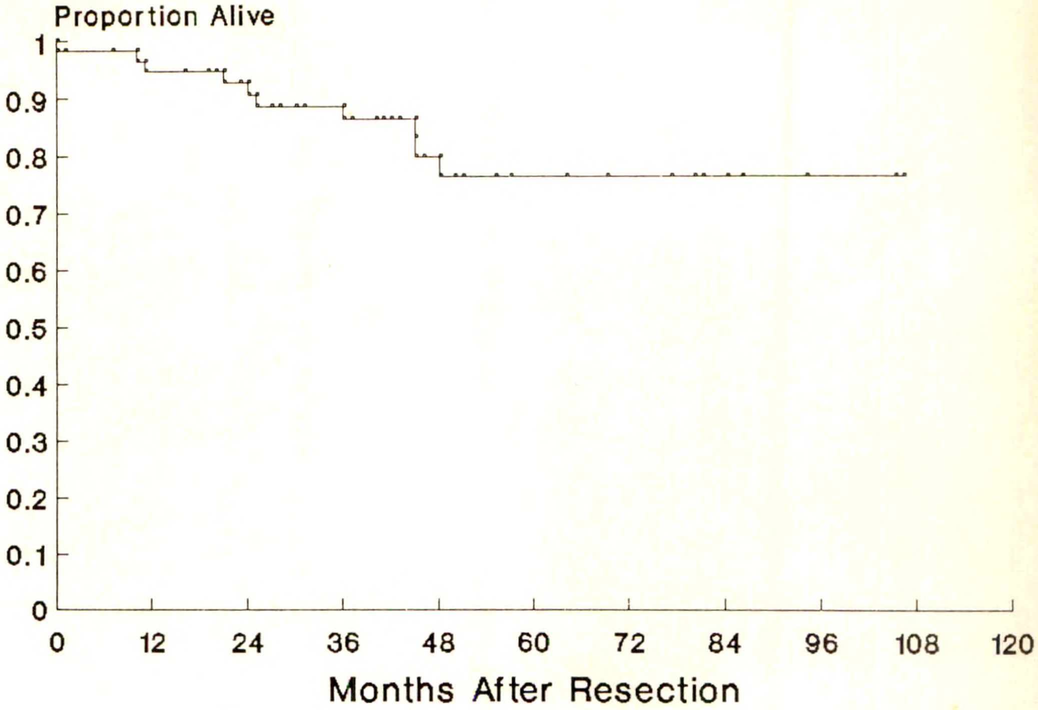

FIG. 1. Disease-free survival distribution of early gastric cancer patients who underwent resection with curative intent at MSKCC 1960–1988 (Kaplan–Meier plot).

consisted of two who had first-echelon (N1) and one who had second-echelon (N2) deposits. Of the two survivors who had N1 disease, one underwent an R2 lymphadenectomy for a diffuse-type, moderately differentiated, excavated tumor that was confined to the mucosa; the other underwent an R1 lymphadenectomy for an intestinal-type, well-differentiated, submucosal excavated tumor that had one microscopic focus of metastatic disease. The surviving patient who had N2 disease underwent an R2 lymphadenectomy for a diffuse-type, well-differentiated, intramucosal excavated lesion (Table 1).

Discussion

Early gastric cancer has been identified as a distinct clinical entity with a high surgical cure rate when com-

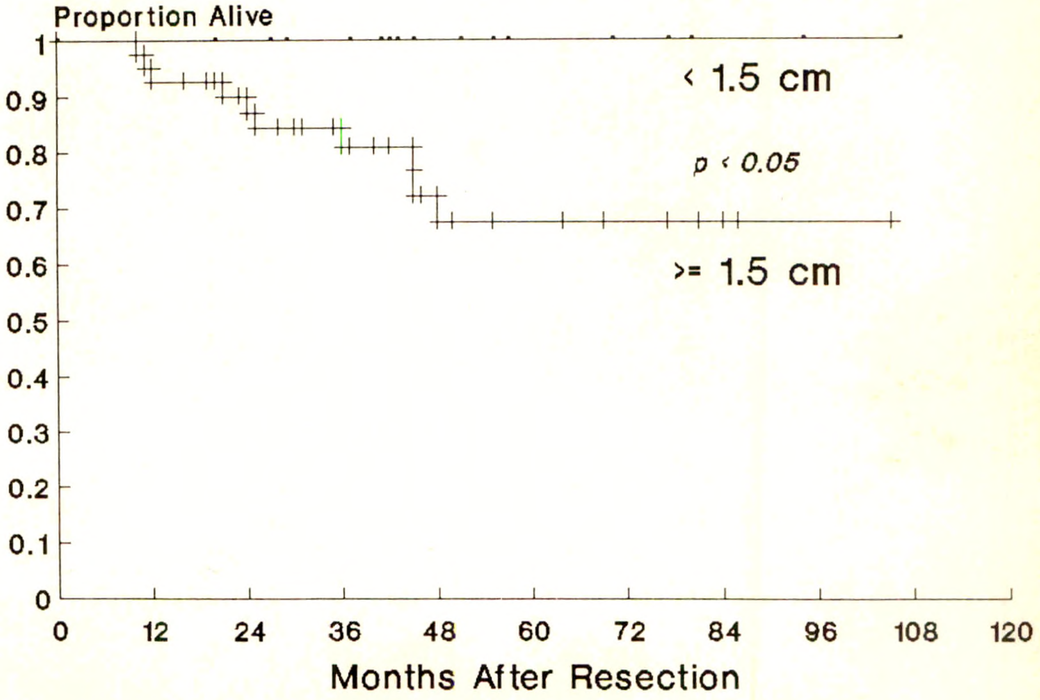

FIG. 2. Postoperative disease-free survival distribution of early gastric cancer patients according to tumor size (diameter in centimeters) (Kaplan–Meier plots).

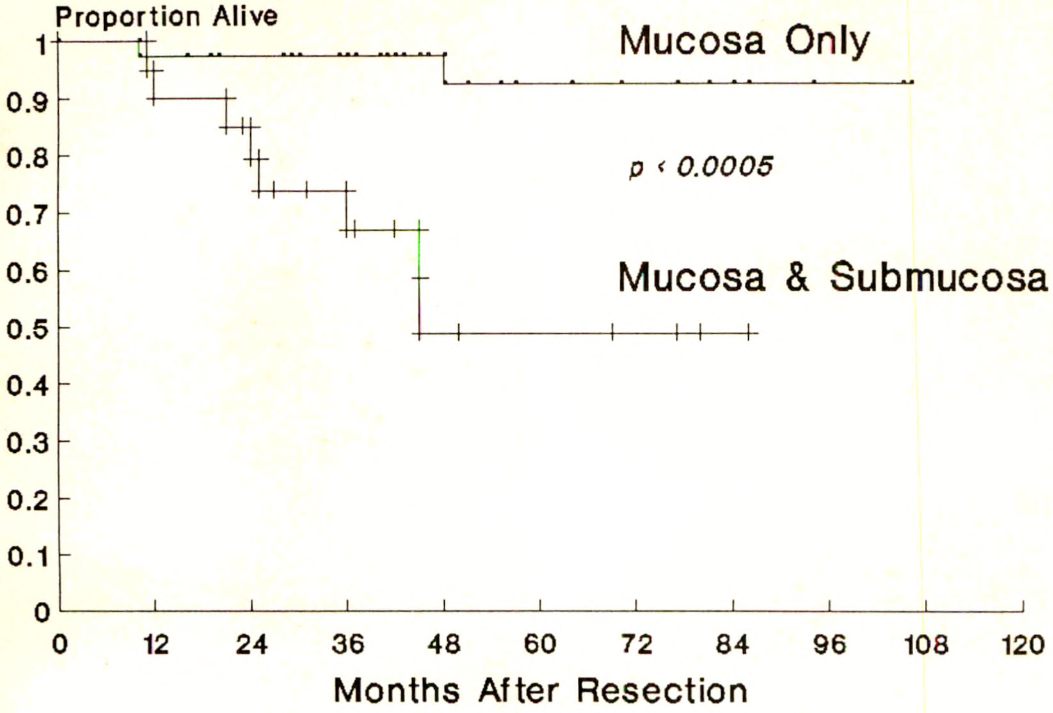

FIG. 3. Postoperative disease-free survival distribution of early gastric cancer patients according to depth of invasion (Kaplan–Meier plots).

pared with advanced gastric cancer. Our experience with these 60 patients treated in New York supports this concept and argues for more aggressive efforts to detect these lesions. Despite declining numbers of gastric cancer cases in this country, the incidence of these early lesions has been increasing in our institution and others since the advent of the fiberoptic gastroscope with capabilities for punch biopsy and brush cytology. Japanese studies suggest that advanced gastric cancer is preceded by the early lesion by about 5 to 10 years. Therefore hope for improved sur-

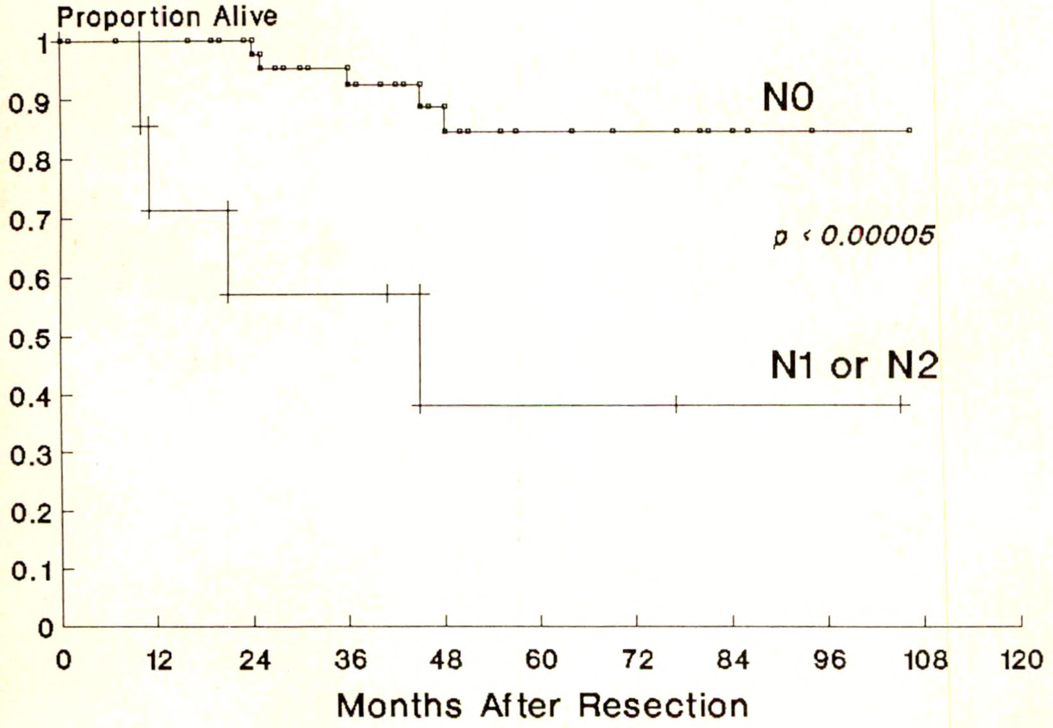

FIG. 4. Postoperative disease-free survival distribution of early gastric cancer patients according to lymph node status. N0, lymph nodes free of metastasis. N1 or N2, metastasis in first or second echelon of regional lymph nodes (Kaplan–Meier plots).

vival in this disease lies in our ability to detect and treat these lesions at an early stage. Because mass screening for this disease is not practical in the United States, other methods of early detection must be sought.

It is evident from this series that a prerequisite for the discovery of an early gastric lesion is the presence of symptoms referable to the upper gastrointestinal tract, *i.e.*, epigastric pain or dyspepsia, because 95% of our patients presented in this manner. Such nonspecific symptoms, particularly during the sixth or seventh decade of life, should not be regarded routinely as benign, non-neoplastic disease and, if persistent, should warrant investigation. In fact more than one third of the patients in this series had pre-existing benign gastric disease that prompted surveillance studies; these studies led to early diagnosis of their cancer. Therefore select screening of high-risk patients, including those with symptoms referable to the upper gastrointestinal tract, and careful follow-up evaluation of patients with seemingly benign gastric disease should improve the detection rate of early gastric cancer.

The diagnostic accuracy of radiographic evaluation was 17% and endoscopic evaluation was 86% in this series. The low yield of radiologic diagnosis is due to the fact that double-contrast thin barium examination was not used routinely. Endoscopy is the procedure of choice and should be performed on all patients in whom the diagnosis of gastric cancer is suspected. Not all early cancers are fluoroscopically visible and minute lesions can be missed even by double-contrast radiography. Malignancy associated with what appeared to be chronic gastric ulcer was prevalent in this series. This observation emphasizes the importance of repeated endoscopy and multiple biopsy specimens in the management of patients with benign gastric lesions, especially because the radiographic and endoscopic appearances of some early gastric cancers may mimic those of benign disease. It is worth remembering that as has been reported by others[15] and also observed in our study, ulcerating gastric carcinomas as well as benign gastric ulcers may heal with the administration of antacids and H2-receptor antagonists.

In our series early gastric cancer assumed many variations in the site, macroscopic appearance, size, and degree of histologic differentiation. However a high incidence of type III excavated lesions was noted and nearly one half of all tumors in our patients were located in the body of the stomach. These two phenomena have been reported in the Japanese literature.[16] Significant prognostic variables found to favor survival in these patients included small tumor size, lack of submucosal invasion, and negative lymph node status. Depth of invasion has been shown to be of the highest prognostic significance, followed by lymph node metastases, in many Japanese and Western studies. Because the small (diameter measuring less than 2 cm), protruded (type I) intramucosal lesions rarely have lymph node metastases, endoscopic resection by cautery snare has been advocated, particularly for elderly patients.[17]

The extent of lymphadenectomy remains a controversial issue in the management of early gastric cancer. In Japan the standard treatment policy for all potentially curable patients with gastric carcinoma is radical resection, including extensive lymphadenectomy. This policy is applied to early as well as advanced gastric cancer; substantial increases in survival time have been reported.[18-20] Approximately 90% of early gastric cancers are reported to be node negative.[10,21] The 5-year disease-free survival rate of node-negative patients was 86.7% in our series. However about 10% of patients in most series of early gastric cancer have shown lymph node metastasis,[10,21] and this was encountered in 8 of 60 patients in our study. Three of these eight patients survived after resection with lymphadenectomy. Two of these eight patients had metastatic deposits in second-echelon (N2) nodes. The risk of lymph node involvement was slightly greater with tumors showing submucosal invasion (23.8%) than with intramucosal lesions (7.7%). Because of the possibility of N2 metastasis, even with accurate knowledge of the depth of invasion (Table 1), selective performance of simple or R1 gastrectomy for mucosal lesions and extended lymphadenectomy (R2) for tumors showing submucosal invasion is not justified. We think an aggressive surgical approach including extended lymphadenectomy should be used for all early gastric cancers if there is potential for cure. The only exception may be the small protruded (type I) intramucosal lesion that can be removed by endoscopic cautery snare, particularly in frail patients. The benefit of extended lymphadenectomy as applied to all stages of curable gastric cancer must be proved by prospective randomized clinical trial. However the surgeon who treats an early gastric cancer needs to consider that even though the cure rate is high, up to 10% of these tumors have lymph node metastases and that such metastases may be present in a second-echelon lymph node. At least for this reason, extended lymphadenectomy (R2) should be performed for these highly curable patients.

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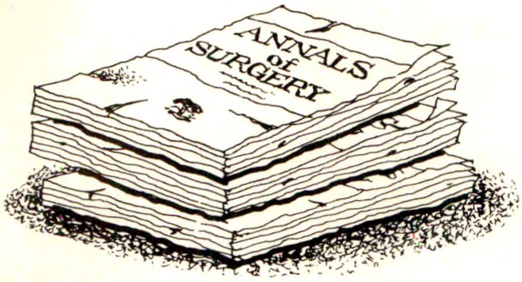

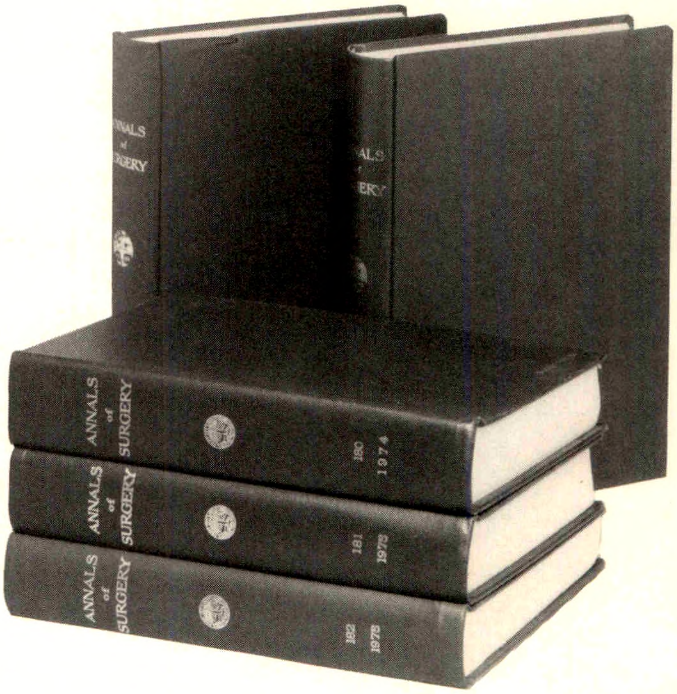

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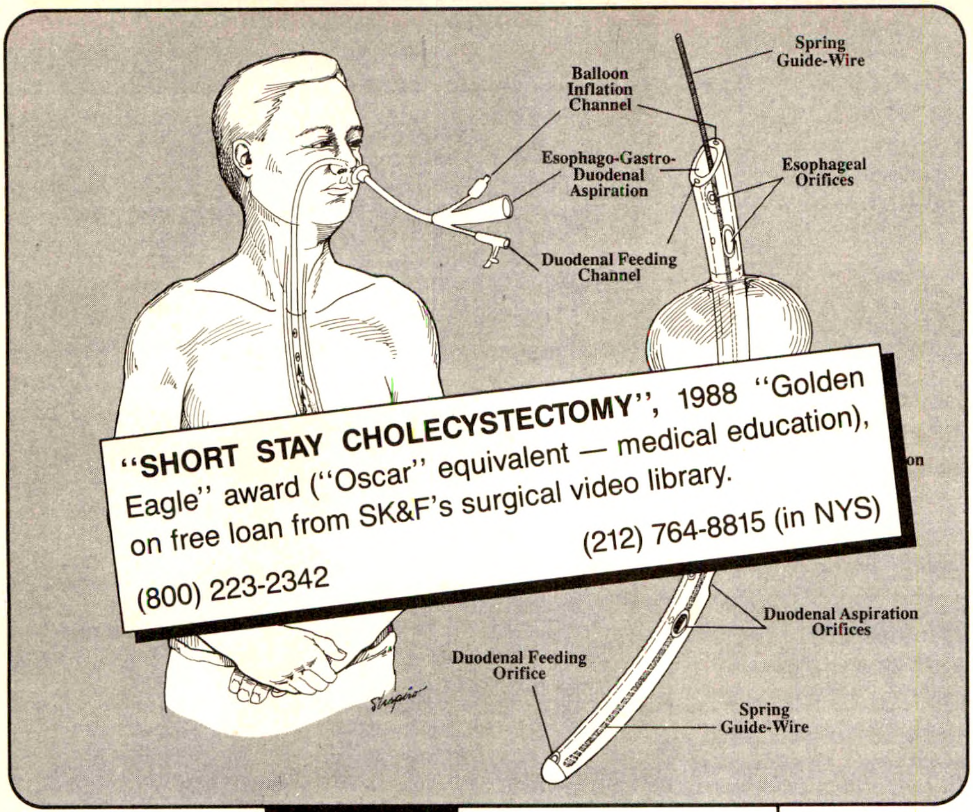

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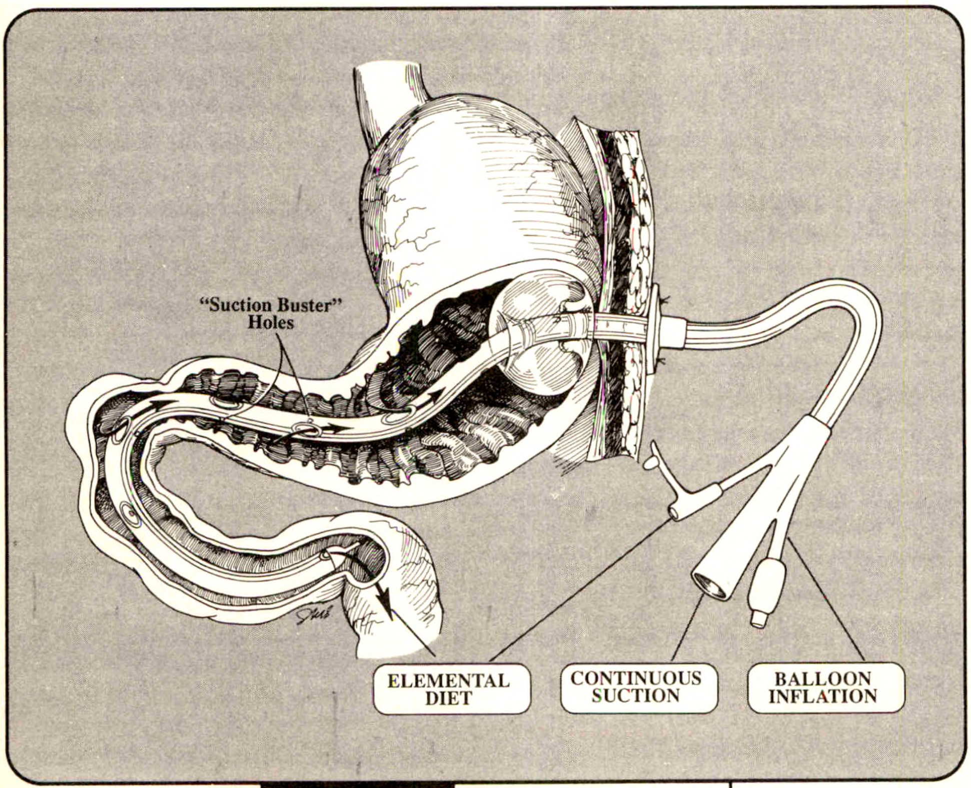

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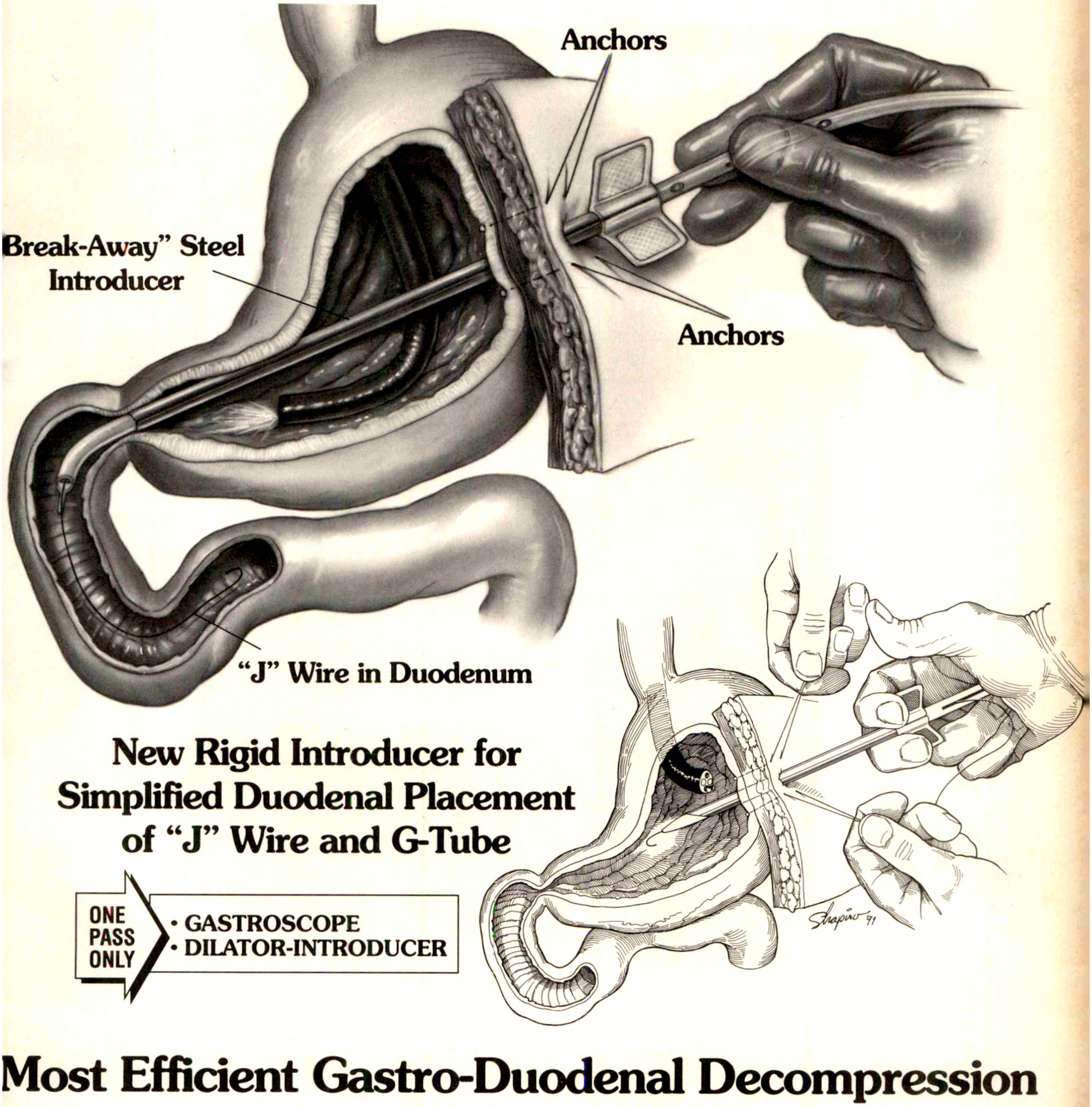

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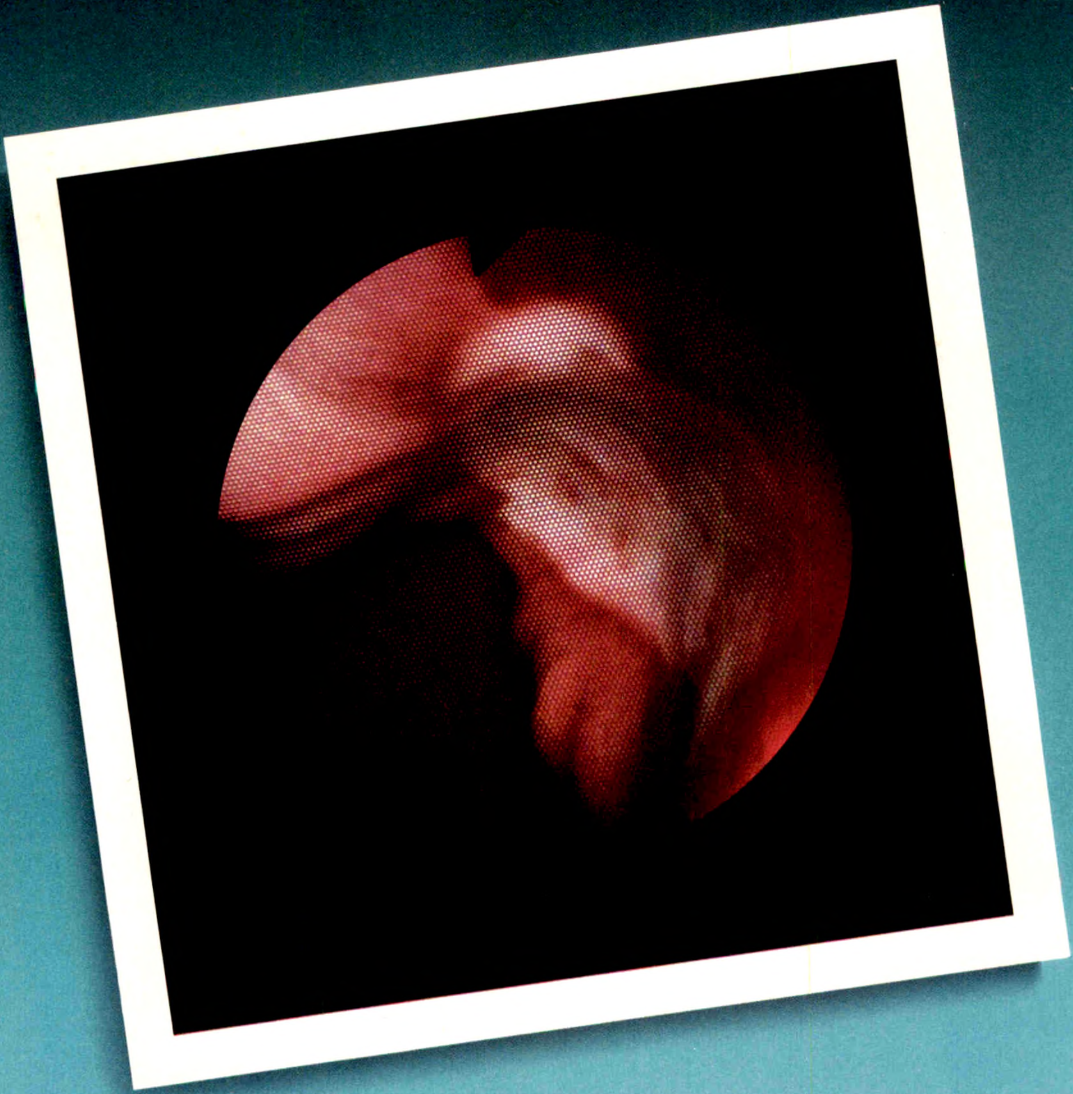

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PEPCID I.V. is indicated in some hospitalized patients with pathological hypersecretory conditions or intractable ulcers or as an alternative to the oral dosage forms for short-term use in patients who are unable to take oral medication.

All formulations of PEPCID are contraindicated in patients who are hypersensitive to any component of these products. PEPCID is usually well tolerated; most adverse reactions have been mild and transient. The following adverse reactions have been reported at a rate greater than 1% of patients on therapy with PEPCID in controlled clinical trials and may be causally related to the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%), and diarrhea (1.7%).

For complete contraindications, warnings, precautions, and adverse reactions, please see the Brief Summary of Prescribing Information on the following page.

1. Ryan, J. R. et al.: Comparison of effects of oral and intravenous famotidine on inhibition of nocturnal gastric acid secretion, Am. J. Med. 81(suppl 4B):60-64, October 24, 1986.
2. Frank, W. O. et al.: The effect of single intravenous doses of cimetidine or ranitidine on gastric secretion, Clin. Pharmacol. Ther. 40(6):665-672, December 1986.

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Precautions: ***General:*** Symptomatic response to therapy does not preclude the presence of gastric malignancy.

Patients with Severe Renal Insufficiency: Longer intervals between doses or lower doses may be needed in patients with severe renal insufficiency (creatinine clearance $<$10 mL/min) to adjust for the longer elimination half-life of famotidine (see Clinical Pharmacology and Dosage and Administration sections of Prescribing Information).

Information for Patients: The oral suspension should be shaken vigorously for 5 to 10 seconds prior to each use, and unused constituted oral suspension should be discarded after 30 days.

Drug Interactions: No drug interactions have been identified. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, aminopyrine, and antipyrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In rats and mice given oral doses up to approximately 2,500 times the recommended human dose for active duodenal ulcer, there was no evidence of carcinogenic potential; at these doses in rats, fertility and reproductive performance were not affected. No evidence of a mutagenic effect was observed.

Pregnancy: *Pregnancy Category B*–There are no adequate or well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether famotidine is secreted into human milk; however, it is secreted into the milk of lactating rats. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use In Elderly Patients: No dosage adjustment is required based on age but may be necessary in severe renal impairment (see Clinical Pharmacology section of Prescribing Information).

Adverse Reactions: The adverse reactions listed below have been reported during domestic and international clinical trials in approximately 2,500 patients. In the placebo-controlled clinical trials, the incidence of adverse experiences with PEPCID Tablets 40 mg at bedtime was similar to that with placebo.

Incidence Greater than 1%: The following adverse reactions have been reported to occur in more than 1% of patients on therapy with PEPCID in controlled clinical trials and may be causally related to the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%), and diarrhea (1.7%).

Causal Relationship Unknown: The following other adverse reactions have been reported infrequently and within each category are listed in order of decreasing severity. The relationship to therapy with PEPCID has been unclear in many cases. *Body as a Whole*–Fever, asthenia, fatigue. *Cardiovascular*–Arrhythmia, AV block, palpitation. *Gastrointestinal*–Cholestatic jaundice, liver enzyme abnormalities, vomiting, nausea, abdominal discomfort, anorexia, dry mouth. *Hematologic*–Rare cases of agranulocytosis, pancytopenia, leukopenia, thrombocytopenia. *Hypersensitivity*–Anaphylaxis, angioedema, orbital or facial edema, urticaria, rash, conjunctival injection. *Musculoskeletal*–Musculoskeletal pain, arthralgia. *Nervous System/Psychiatric*–Grand mal seizure; psychic disturbances, which were reversible in cases for which follow-up was obtained, including hallucinations, confusion, agitation, depression, anxiety, decreased libido; paresthesia; insomnia; somnolence. *Respiratory*–Bronchospasm. *Skin*–Alopecia, acne, pruritus, dry skin, flushing. *Special Senses*–Tinnitus, taste disorder. *Other*–Rare cases of impotence have been reported; however, in controlled clinical trials, the incidence was not greater than that seen with placebo.

The adverse reactions reported for PEPCID Tablets may also occur with PEPCID Oral Suspension or PEPCID I.V.; in addition, transient irritation at the injection site has been observed with PEPCID I.V.

Management of Overdosage: There is no experience to date with deliberate overdosage. Up to 640 mg/day have been given to patients with pathological hypersecretory conditions with no serious adverse effects. In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

Dosage and Administration: ***Duodenal Ulcer:*** The recommended adult oral dosage for active duodenal ulcer is 40 mg h.s.; most patients heal within 4 weeks, and it is rarely necessary to use the full dosage for longer than 6 to 8 weeks. A regimen of 20 mg b.i.d. is also effective. For maintenance therapy, the recommended oral dosage is 20 mg h.s.

Benign Gastric Ulcer: The recommended adult oral dosage for active benign gastric ulcer is 40 mg h.s.

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas): The dosage varies with the individual patient; the recommended adult oral starting dosage is 20 mg q6h, but some patients may require a higher starting dosage. Dosages should be adjusted to individual patient needs and continued as long as clinically indicated; up to 160 mg q6h have been administered to some patients with severe Zollinger-Ellison syndrome.

Oral Suspension: The oral suspension may be substituted for tablets.

Directions for Preparing PEPCID Oral Suspension: Prepare suspension at time of dispensing. Slowly add 46 mL Purified Water. Shake vigorously for 5 to 10 seconds immediately after adding the water and immediately before use.

Stability of PEPCID Oral Suspension: Unused constituted oral suspension should be discarded after 30 days.

Intravenous Administration: In some hospitalized patients with pathological hypersecretory conditions or intractable ulcers or in patients who are unable to take oral medication, the recommended intravenous dosage is 20 mg q12h. For preparation of intravenous solutions for injection or infusion and for compatible diluents, please see Prescribing Information. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Concomitant Use of Antacids: Antacids may be given concomitantly if needed.

Dosage Adjustment for Patients with Severe Renal Insufficiency: In patients with severe renal insufficiency (creatinine clearance less than 10 mL/min), the elimination half-life of famotidine may exceed 20 hours, reaching approximately 24 hours in anuric patients. Although no relationship of adverse effects to high plasma levels has been established, to avoid excess accumulation of the drug, the dosage may be reduced to 20 mg h.s. or the dosing interval may be prolonged to 36 to 48 hours as indicated by the patient's clinical response.

How Supplied: Tablets, containing 20 mg or 40 mg famotidine, with hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, starch, talc, and titanium dioxide as inactive ingredients, in unit-of-use bottles of 30 and 100 and unit-dose packages of 100; Oral Suspension, containing 40 mg famotidine per 5 mL after constitution with 46 mL Purified Water, with citric acid, flavors, microcrystalline cellulose and carboxymethylcellulose sodium, sucrose, and xanthan gum as inactive ingredients, and sodium benzoate 0.1%, sodium methylparaben 0.1%, and sodium propylparaben 0.02% added as preservatives, in bottles of 400 mg famotidine for constitution; Solution for intravenous injection, containing 10 mg famotidine per mL, with L-aspartic acid 4 mg, mannitol 20 mg, and Water for Injection q.s. 1 mL as inactive ingredients, and benzyl alcohol 0.9% added as preservative to the multidose vial, as 10x2-mL single-dose vials and as 4-mL vials.

For more detailed information, consult your MSD Representative or see Prescribing Information.

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Biliary Response to Glucagon in Humans

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From the Department of Surgery, Duke University and Veterans Administration Medical Centers, Durham, North Carolina

Glucagon has been demonstrated to have profound effect on biliary secretion in several species. Glucagon's biliary effects were studied in humans following biliary tract surgery. Nine patients underwent common bile duct exploration and insertion of a balloon-occludable t tube. An aliquot of the collected sample was kept and the enterohepatic circulation was maintained by reinfusion of the collected bile *via* the distal t-tube port. Glucagon increased bile flow and decreased cholesterol and phospholipid output during stable bile acid output. Furthermore high-performance liquid chromatographic analysis of bile acid profiles revealed no significant changes in bile salt species or conjugation after glucagon infusion. Glucagon is probably important in the physiologic regulation of biliary secretion in humans.

HEPATIC BILIARY SECRETION is a complex process with several steps that are energy dependent and other components, such as paracellular flow, that are more simple. A fraction of bile flow depends on active secretion of bile salts from the hepatocyte, while the bile canaliculus also secretes a fraction of bile that is seemingly independent of bile salt secretion. Canalicular bile then undergoes significant modification in the biliary ductules principally involving secretion and absorption of electrolytes. Classically biliary cholesterol secretion is a passive process closely linked to the solvent properties of bile acid and phospholipid. Several factors that influence these processes are known, but a great deal remains to be learned regarding their regulation.

Glucagon increases the secretion of large, inert markers such as erythritol into bile in several species including dogs, cats, and humans.[1-3] Such data indicate that glucagon stimulates the bile acid-independent fraction of canalicular bile secretion. In addition glucagon decreases cholesterol and phospholipid secretion at physiologic doses.[4,5] A variety of evidence suggests that glucagon is physiologically important in the regulation of biliary secretion in animals.[2,4-6] Evidence that glucagon might be important in humans include glucagon's other hepatic effects such as on glucose metabolism, hepatic extraction of glucagon,[7] and a preliminary investigation suggesting that this might be so.[2] Whether glucagon influences the secretion of specific bile acids has not been studied in humans. The following experiments were performed to study the effects of glucagon on bile flow and composition in the intact human liver.

Methods

Nine adult patients underwent biliary tract surgery. A triple-lumen t tube with a distal inflatable balloon was placed at the time of surgery to permit complete diversion and reinfusion of bile. The patients were studied for a minimum of 8 days after surgery, at which time they were tolerating a regular diet and had normal liver function tests. The t tubes had been clamped for at least 3 days and biliary tract integrity was confirmed by t-tube cholangiogram. After an overnight fast, studies were performed in random order on successive days. Throughout each experiment, 0.9% sodium chloride was infused at 60 mL/hour *via* a peripheral vein. The common bile duct was occluded by inflation of the t-tube balloon, and bile was collected in 15-minute periods. A small quantity was kept for analysis and the remainder was reinfused through the distal port to maintain an intact enterohepatic circulation.

These studies were supported by NRSA grant DK08155, Veterans Administration research funds, NIH General Clinical Research Centers Program, National Center for Research Resources, M01-RR-30, and by NIH grant DK35490.

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Following four 15-minute periods, patients received a 2-hour infusion of either glucagon (2 μg/kg/hr) or sodium chloride 0.9%. Peripheral blood samples were drawn hourly in iced tubes and immediately processed and stored at −20°C for later analysis. Samples for glucagon analysis contained 4.2 μg aprotinin (Sigma Chemical Co., St. Louis, MO). All patients were studied under control and experimental conditions.

Bile volumes were measured to the nearest 0.1 mL. Bile acid concentration was determined by the 3-alpha-hydroxysteroid method using sodium taurocholate and the standard.[8] Biliary lipids were extracted using the method of Folch[9] and total phospholipids were quantified using a modified method of Fisk and Subbarow.[10] Biliary cholesterol was determined by the method of Abell et al.[11]

Plasma glucose was determined using a Beckman glucose analyzer (Beckman Instruments, Palo Alto, CA). Radioimmunoassay for glucagon was performed using Unger's 30-K antiserum after the method of Unger et al.[12] Insulin radioimmunoassay was performed using a modification of the double-antibody procedure of Morgan and Lazarow.[13]

High-performance liquid chromatography was used to determine the profiles of conjugated bile acids. Samples were analyzed after the method of Rossi et al.[14] using Sep-Pak (Waters Co., Milford, MA) absorption of 50-μL samples with PO_4 buffer at pH 7 followed by Waters 8-mm μbondpak C-18 column at 201-nm wave length for 36 minutes.

Statistical analysis of data was performed between preinfusion and experimental periods and between experiments using the t test for paired values. The experimental protocol was approved by the Committee on Human Experimentation and informed consent was obtained from each patient.

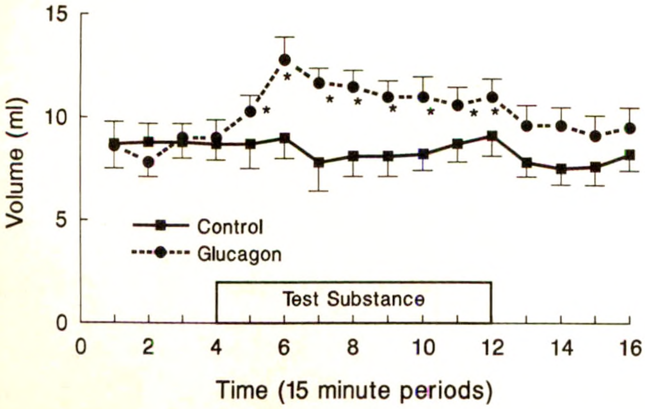

FIG. 1. Bile flow increased after glucagon infusion and returned toward baseline immediately after the infusion was stopped (* denotes $p < 0.05$ compared to preinfusion value).

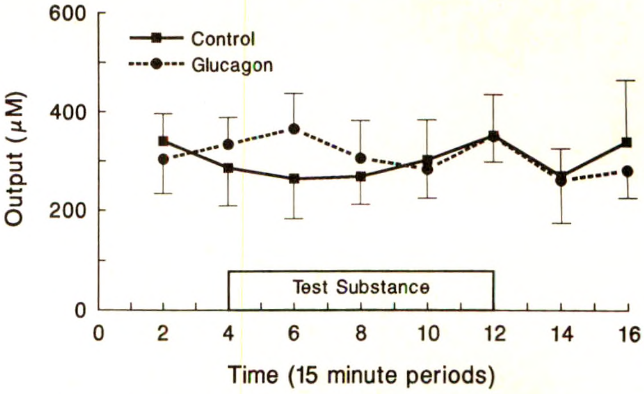

FIG. 2. Bile acid output was variable among patients and did not change significantly during glucagon infusion.

Results

Bile Flow

Bile flow increased significantly in all patients within 30 minutes of the onset of glucagon infusion (Fig. 1). Flow increased from a baseline of 9 ± 0.9 mL/15 min. in the fourth period to a peak of 12.8 ± 1.1 mL/15 min. 30 minutes after infusion began. Bile flow promptly returned to baseline after cessation of glucagon infusion. Bile flow did not change from baseline during saline infusion and was significantly lower than with glucagon infusion in all test periods.

Bile Acid

Bile acid concentration decreased significantly during glucagon infusion from 39 ± 8 μmol/L (micromolar)/mL in period 4 to a trough of 22 ± 6 μmol/L/mL in period 13 (Fig. 2). Bile acid output varied widely among patients, but total bile acid output did not change significantly during glucagon infusion. Bile acid concentration and output did not change during saline infusion, but the concentration was significantly higher in the saline than glucagon group in periods 7 through 12.

Bile Acid Profiles

Bile samples from four patients (eight studies) were analyzed for conjugated bile acid profiles (Table 1). Conjugates of primary bile acids predominated in all samples (range, 90% to 99%). Glycine conjugates (79% to 95%) were more abundant than taurine (5% to 21%), and the glycine:taurine ratio ranged from 3.76 to 19 among samples.

The predominant bile acids in all samples were glycocholic acid (44% to 73%) and glycochenodeoxycholic acid (17% to 41%). Taurocholic and taurochenodeoxycholic acids were found in all other samples, comprising

TABLE 1. *Bile Acid Profile During Control and Glucagon Experiments (n = 4)*

Experiment	Period	% Primary Bile Acids	% Glycine Conjugates	% GLC	% GCDC
Control	1	96.2 ± 1.8	88.0 ± 3.2	58.5 ± 62	26.0 ± 3.4
	7	95.5 ± 2.3	89.5 ± 3.0	61.5 ± 5.7	23.0 ± 3.8
	15	96.3 ± 1.5	88.8 ± 3.4	56 ± 5.1	29.5 ± 1.9
Glucagon	1	95.8 ± 1.9	89.8 ± 1.7	57.8 ± 4.5	29.3 ± 3.5
	7	95.8 ± 1.9	90.0 ± 2.0	57.3 ± 3.4	30.3 ± 2.6
	15	95.5 ± 2.5	91.8 ± 1.9	58.5 ± 4.3	33.3 ± 4.8

GDC, glycocholic acid; GCDC, glycochenodeoxycholic acid.

1% to 11% of total bile acids. Glycodeoxycholic acid was found in all samples of two patients (1% to 7%) but was not found in the two others. Trace amounts of other secondary and tertiary bile acids were found in most samples.

No significant changes were noted in the percentage of primary bile acids, glycine to taurine ratio, or fraction of the various bile acids before and after glucagon infusion, or between the glucagon and saline groups.

Cholesterol

Cholesterol concentration decreased significantly from 129 ± 14 mg/dL in period 4 to 76.4 ± 6.3 mg/dL in period 8 and remained decreased throughout all remaining periods (Fig. 3). Cholesterol output decreased significantly from 11.8 ± 2.0 mg/15 min. in period 4 to 8.8 ± 1.0 mg/15 min. in period 8, and it decreased further through all remaining periods. Neither cholesterol concentration nor output changed with saline infusion. Cholesterol concentration was higher during saline infusion in periods 8, 10, and 12 as compared to glucagon infusion.

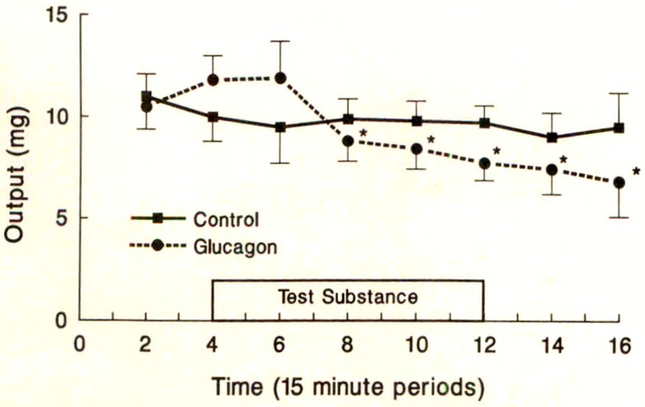

FIG. 3. Biliary cholesterol output decreased significantly during glucagon infusion, and continued to decline after the infusion was stopped (* denotes $p < 0.05$ compared to preinfusion value).

Phospholipid

The phospholipid concentration decreased significantly with glucagon infusion from 45.0 ± 15.0 mg/dL in period 4 to 31.0 ± 13.0 mg/dL in period 8 (Fig. 4). The total phospholipid output decreased significantly with glucagon infusion from 41.5 ± 19.3 mg/15 min. to 31.4 ± 13.2 mg/15 min. in periods 4 and 12, respectively. There was no change in phospholipid concentration or output during saline infusion.

Glucose

Serum glucose (Fig. 5) increased significantly with glucagon infusion from 107 ± 9 mg/dL in period 4 to 152 ± 28 mg/dL in period 8 (Table 2.). Following the cessation of glucagon infusion, glucose levels returned to baseline within 1 hour. The peak increase represented an increase of 53% above baseline. Glucose levels were unchanged during saline infusion.

Glucagon

Serum glucagon (Fig. 5) increased as expected during infusion from 163 ± 0 pg/mL in period 4 to 1763 ± 205 pg/mL in period 12 (Table 2). Levels returned to baseline within 1 hour after the glucagon infusion was stopped. Glucagon levels were unchanged during saline infusion.

Insulin

In all patients serum insulin (Fig. 5) levels increased during glucagon infusion (from 43 ± 7 αU/mL in period 4 to a peak of 142 ± 40 αU/mL in period 8) (Table 2). Levels of serum insulin remained stable throughout saline infusion.

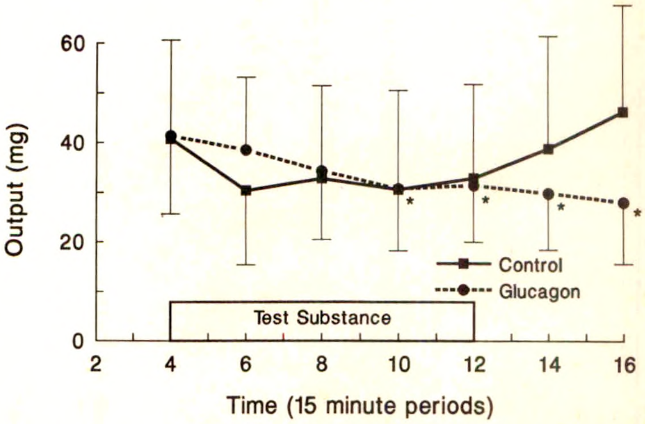

FIG. 4. Biliary phospholipid output decreased significantly during glucagon infusion and continued to decline after the infusion was stopped (* denotes $p < 0.05$ compared to preinfusion value).

TABLE 2. *Serum Glucose and Hormone Profiles During Control and Experimental Conditions (n = 5)*[1]

	Per 4	Per 8	Per 16
Control			
Glucose (mg/dL)	96 ± 6	95 ± 8	95± 8
Glucagon (pg/mL)	140 ± 22	141 ± 20	158 ± 23
Insulin (μU/mL)	43 ± 6	41 ± 7	42 ± 7
Glucagon			
Glucose (mg/dL)	107 ± 8	152 ± 23*	104 ± 22
Glucagon (pg/mL)	163 ± 40	1683 ± 318†	598 ± 336
Insulin (μU/mL)	45 ± 8	142 ± 41[2]	139 ± 60

* $p = 0.05$; † $p = 0.003$

[1] Glucagon infusion 2 $\mu g\ kg^{-1} \cdot hr^{-1}$ during periods 5 to 12.

[2] $p = 0.059$. A large standard deviation prevents statsitical significance.

Discussion

These data extend previously reported observations in a single patient that intravenously infused glucagon has profound effects on hepatic bile production and composition.[2] Glucagon increased bile flow during stable bile acid output, supporting data from other species and humans that glucagon stimulates the bile acid 'independent' fraction of canalicular secretion.[15-17] Further evidence that glucagon's effects are bile acid independent is contained in the detailed bile acid analysis. In addition glucagon infusion resulted in decreased secretion of biliary cholesterol and phospholipid.

Previous work from this laboratory in patients whose livers were denervated by orthotopic transplantation yielded similar results, indicating a mechanism independent of the sympathetic or parasympathetic nervous systems.[18] Kaminski et al.[6] recently demonstrated the choleretic effect of endogenous glucagon, which was stimulated by amino acid administration. In his studies, however, a fraction of the choleresis noted could not be attributed to glucagon based on comparisons of plasma glucagon levels. It was speculated that the concomitant increase in serum insulin caused by the amino acid administration accounted for a portion of the choleresis seen. Schirmer et al.[4] demonstrated that glucagon was choleretic in the dog at physiologic doses independent of insulin. Furthermore cholesterol was significantly suppressed by such doses, although no decrease in phospholipid output was seen. Garberoglio et al.[5] demonstrated in the dog that glucagon infusion at doses yielding approximately postprandial levels caused a choleresis and suppressed cholesterol and phospholipid output. Exogenous glucagon produces chloride-rich bile secondary to enhanced chloride secretion or decreased ductular absorption.

The mechanism of glucagon's choleretic action remains unclear despite intense investigation. It is postulated that glucagon exerts its effect through a second messenger,

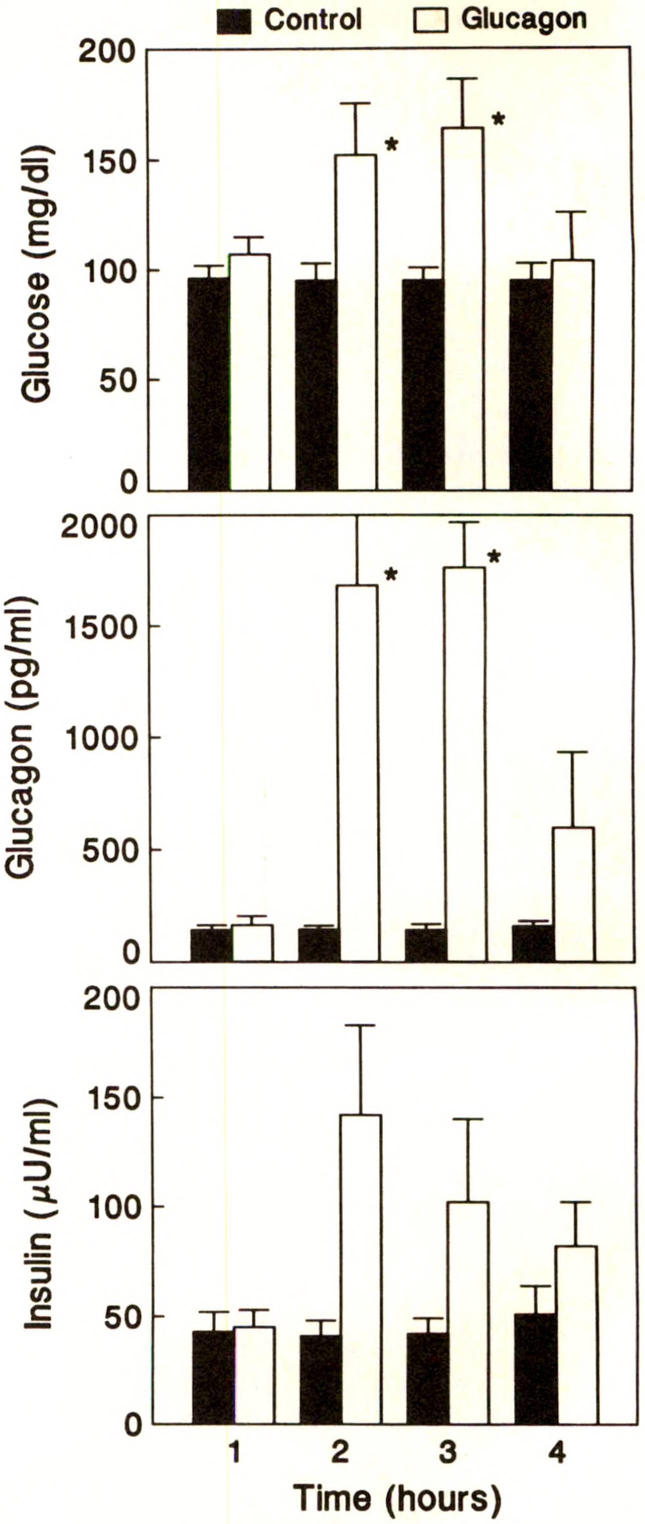

FIG. 5. Serum glucose (top), glucagon (middle), and insulin (bottom) levels. Glucagon or saline was infused during hours 2 and 3. There were significant increases in serum glucose and glucgon during the infusion, which promptly returned toward baseline. Serum insulin increased in all patients (n = 5), but did not reach statistical significance. (* denotes $p < 0.05$ compared to preinfusion value).

cyclic adenine monophosphate (AMP). Evidence to support this theory is found in data demonstrating that glucagon effects are mimicked by the infusion of dibutyryl cyclic AMP infusion in the cat and dog.[3,19] At issue is whether cyclic AMP decreases cholesterol synthesis or decreases cholesterol delivery into the canaliculus. Studies to resolve this question have not, as yet, been performed in humans. Support for a direct effect by glucagon on biliary secretion from hepatocytes has been shown in isolated perfused liver systems of the rat, guinea pig, rabbit, and other species.[20-22]

Recent data raise the possibility that glucagon may alter the way in which cholesterol is processed within the hepatocyte. Chronically administered glucagon increases the production and enterohepatic circulation of bile acids while decreasing the activity of hydroxymethylglutaryl coenzyme A reductase.[23] This finding suggests that glucagon might 'shunt' cholesterol into bile acid synthesis. In addition glucagon administration has been shown in rats to stimulate autophagy, the process by which hepatocyte lysosomes disassemble intracellularly derived materials.[24] Such stimulation was shown to decrease markedly lysosomal protein excretion into bile, although little effect was shown on lipid secretion in the rat. The possibility is raised, however, that decreased lysosomal excretion could explain, in part, the demonstrated decrease in cholesterol output.

Glucagon's coregulator of glucose homeostasis, insulin, also has been shown to induce choleresis in various species. Because glucagon infusion in this study caused hyperinsulinemia, it is impossible to exclude this as a contributory factor in the choleresis seen. However insulin infusion at doses that cause higher serum insulin levels than the glucagon infusion in these studies was not choleretic in transplant patients and induced no suppression of lipid secretion.[18] A synergistic effect of glucagon and insulin infusion was demonstrated in previous work, however, and such a synergism cannot be excluded in the present study.

Theoretically glucagon could alter the uptake or transport of various bile acids across the hepatocyte. If such effects resulted in the differential secretion of more hydrophilic bile acid species, glucagon's choleretic effect could be classified as a bile acid-dependent phenomenon. The high-performance liquid chromatography bile acid profiles in these patients demonstrated no significant dilution or alteration of species of secreted bile acids. These findings lend further support to the theory that glucagon's choleretic effect is independent of canalicular bile acid secretion. In addition it is doubtful that the decreased lipid output can be explained by canalicular dilution of bile salt, in which case the phospholipid to cholesterol ratio would have remained constant. The data clearly show more significant suppression of cholesterol (35%) than phospholipid (24%), an observation consistent with those seen in the previous intact patient,[2] as well as in the transplant group.[18]

In summary glucagon induced choleresis and suppressed biliary lipid secretion in patients with intact livers at the dose tested. In addition bile salt secretion remained stable and the profile of conjugated bile acids remained unchanged before and after glucagon infusion. These data support a possible role for glucagon as a modifier of bile formation and show that glucagon stimulates the bile acid-independent fraction of canalicular secretion in humans.

Acknowledgments

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Changes in High-energy Phosphate Metabolism and Cell Morphology in Four Models of Acute Experimental Pancreatitis

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Previous studies using the isolated *ex vivo* perfused canine pancreas preparation showed that during a 4-hour perfusion pancreatitis (edema, weight gain, hyperamylasemia) can be induced by four different stimuli. The stimuli include the intra-arterial infusion of oleic acid (FFA), a 2-hour period of ischemia before perfusion (ISCH), partial obstruction of the pancreatic duct with secretin stimulation (POSS), and the intra-arterial infusion of cerulein at supramaximal doses (CER). In the present study, changes in high-energy phosphate metabolism, as determined by nuclear magnetic resonance spectroscopy, and changes in cellular structure, determined by light and electron microscopy, were documented for all four models of acute pancreatitis. The control preparations remained stable for the 4-hour perfusion period, with no decrease in adenosine triphosphate (ATP) levels. In the FFA preparations, ATP decreased to 36% of baseline levels during the 4-hour perfusion ($p < 0.001$). In the ISCH preparations, ATP decreased to undetectable levels during the 2-hour period of ischemia, but recovered rapidly and remained at baseline levels during the perfusion. ATP levels remained stable in the remaining two models of pancreatitis (POSS, CER). Microscopy demonstrated that the initial injury was located chiefly in the capillaries (swollen endothelium, intravascular thrombi) in the FFA and ISCH preparations. In the POSS and CER preparations, capillary changes were minimal and the injury was located chiefly in the acinar cells (swollen endoplasmic reticulum, zymogen granule depletion, vacuolization). The POSS preparations also showed striking dilation of centroacinar lumens reflecting duct obstruction. In additional studies it was shown that the ATP decline in the FFA preparations could be significantly reduced by pretreatment with free radical scavengers. The morphologic changes could be reduced by free radical scavengers in the FFA and ISCH preparations. Any amelioration of morphologic injury in the POSS preparations was obscured by dilatation of centroacinar lumens in both treated and untreated groups. The morphologic changes in the CER preparations were reduced by treatment with a cholecystokinin inhibitor.

ACUTE PANCREATITIS CAN be initiated in the isolated perfused *ex vivo* canine pancreas preparation by four markedly disparate stimuli.[1-4] These stimuli are the intra-arterial infusion of oleic acid (FFA), a 2-hour ischemic period before perfusion (ISCH), partial obstruction of the pancreatic duct with secretin stimulation (POSS), and the infusion of cerulein at a supramaximal stimulatory rate (CER). In all four models of pancreatitis, the physiologic injury response is similar, with edema, weight gain, and hyperamylasemia. In an effort to understand the injury response on a subcellular level, changes in high-energy phosphate metabolism and in cell morphology were followed in all four models of acute pancreatitis during a 4-hour perfusion period. The injury response in these four models has been shown previously to be ameliorated by free radical scavengers or by a cholecystokinin receptor antagonist.[5,6] High-energy phosphate metabolism and cellular morphology also were recorded in these four models of acute pancreatitis when treated with free radical scavengers or with a cholecystokinin inhibitor.

Materials and Methods

Experimental Preparation

Adult mongrel dogs weighing between 18 and 23 kg were anesthetized with sodium pentobarbital. The pancreas was removed and placed in a perfusion circuit in a humidified chamber, as previously described.[1] The perfusate consisted of 400 mL of autologous blood, 100 mL of Ringer's lactate solution, 0.5 g of glucose, 2.5 g of human albumin, and 15 mEq of sodium bicarbonate. An

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additional 0.25 g of glucose was administered after 2 hours of perfusion to maintain the glucose level in the perfusate over 70 mg/dL. An additional 1 or 2 mEq of sodium bicarbonate was administered when needed to maintain the pH level within the physiologic range (7.37 to 7.54).

The pancreas was perfused through the splenic and superior mesenteric arteries at a constant flow (17 mL/100 g of tissue/min.). The perfusate was collected in a venous reservoir *via* a cannula in the portal vein. From the reservoir the perfusate drained by gravity into a Harvey^R infant oxygenator (C. R. Bard Inc., Billerica, MA) before being pumped back into the preparation. The temperature of the perfusate was maintained at 37°C with a heat exchanger.

The preparation was perfused initially during a 30-minute stabilization period, before the 4-hour study perfusion. During this 4-hour perfusion period, the preparation was monitored continuously and recorded hourly for gross appearance, weight, and arterial blood pressure. Samples of the perfusate were taken from the venous line after the 30-minute stabilization period (time 0), and hourly thereafter to assay for hematocrit, glucose level (automatized blood sugar analyzer, Beckman 2, Fullerton, CA) and amylase activity (AmyloTube^R, Pharmacia Diagnostics Inc., Fairfield, NJ,). Samples of the perfusate were taken from the arterial line at the same intervals to determine hemoglobin, pH, and blood gases (OSM 2 Hemoximeter and Acid-Base Analyzer^R, Radiometer, Copenhagen, Denmark). Pancreatic juice was collected hourly *via* a 16 gauge cannula in the pancreatic duct.

When monitoring high-energy phosphate metabolism by magnetic resonance spectroscopy (MRS), the preparations were placed into the bore of a 4.7 T magnet of a spectrometer (General Electric, Fremont, CA). Phosphorus-31 spectra were obtained at 81 MHz, with a three-turn surface coil placed away from the duodenal cuff, on the body, head, and uncinate process of the gland. The data were collected for 14.5 minutes for one spectrum. The first baseline spectrum was obtained during the 14.5 minutes before time 0, and the 16 consecutive study spectra during the 4-hour perfusion period after time 0. The concentrations of ATP and inorganic phosphate (P_i) were calculated as the areas of the respective signals in the spectrum and were related to the area of the phosphomonoester signal.

In the preparations monitored for morphologic changes, tissue specimens were obtained for microscopy at time 0, and after 1 hour and 4 hours of perfusion. The specimens were taken from the same site of the pancreas in each preparation. The 1-mm^3 pieces were fixed overnight in 3% glutaraldehyde in phosphate buffer (pH 7.4), followed by 1% osmium tetroxide after fixation. The specimens were embedded in Araldite (Electronmicroscopy Sciences, Fort Washington, PA). Thick sections (1 μm) were stained with toluidine blue for light microscopy and thin sections (60 to 90 nm) were stained with uranyl acetate and lead citrate for transmission electron microscopy. Thick sections of four treated and four untreated preparations stained with toluidine blue were ranked for acinar cell injury within each of the four models of pancreatitis without knowledge of the treatment status. Three sections from each preparation were examined for degree of zymogen depletion and number of vacuoles. The eight preparations for each model were then ranked from most severe (rank 1) to least severe (rank 8) injury.

To compare the results between groups, Student's t test and variance analysis were used.

Experimental Protocol

Untreated groups I–V.

Group I: Controls (12 preparations). These preparations were perfused for 4 hours after the initial 30-minute stabilization period. Eight preparations were monitored for phosphorus-31 by MRS and specimens for microscopy were obtained from four preparations.

Group II: Oleic acid (FFA) (12 preparations). These preparations were managed identically to those in group I, except that 0.15 mL of oleic acid (Sigma Chemical Co., St. Louis, MO) was infused into the arterial line over the first hour starting at time 0. Eight preparations were monitored for phosphorus-31 spectra by MRS and specimens for microscopy were obtained from four preparations.

Group III: Ischemia (ISCH) (nine preparations). After the 30-minute stabilization period, the perfusion circuit was changed to bypass the preparation for 2 hours. Thereafter the perfusion was reconnected and continued for 4 hours. The start of the 4-hour perfusion was designated time 0. Five preparations were monitored for phosphorus-31 spectra by MRS and specimens for microscopy were obtained from four preparations.

Group IV: Partial duct obstruction with secretin stimulation (8 preparations). In these preparations the pancreatic duct was partially obstructed at time 0 by inserting a 25 gauge cannula, partially obstructed with 3–0 steel wire, into the pancreatic duct. In addition 30 units of secretin (Ferring Laboratories Inc., Suffern, NY) were administered at time 0, and 10 units thereafter hourly throughout the 4-hour perfusion. Four preparations were monitored for phosphorus-31 spectra by MRS and specimens for microscopy were obtained from four preparations.

Group V: Cerulein (CER) (eight preparations). These preparations were managed identically to those in group I, except that cerulein (Peninsula Laboratories Inc., Belmont, CA) was infused (20 ng/g of tissue/hr in 0.9% saline) into the arterial line during the 4-hour perfusion period starting at time 0. Four preparations were monitored for phosphorus-31 spectra by MRS and specimens for microscopy were obtained from four preparations.

Treated groups VI–IX.

Group VI: FFA + SOD + CAT (12 preparations). These preparations were managed identically to those in group II (FFA), except that 50 mg of bovine erythrocyte superoxide dismutase (SOD) (Sigma Chemical Co.) and 50 mg of bovine liver catalase (CAT) (Calbiochem Corp., La Jolla, CA) were added to the perfusate 15 minutes before time 0. Eight preparations were monitored for phosphorus-31 spectra by MRS and specimens for microscopy were obtained from four preparations.

Group VII: ISCH + SOD + CAT (four preparations). These preparations were managed identically to those in group III (ISCH), except for the administration of SOD and CAT as in group VI. Specimens for microscopy were obtained from all four preparations.

Group VIII: POSS + SOD + CAT (four preparations). These preparations were managed identically to those in group IV (POSS), except for the administration of SOD and CAT as in group VI. Specimens for microscopy were obtained from all the four preparations.

Group IX: CER + L364,718 (four preparations). These preparations were managed identically to those in group V (CER), except for the infusion of a cholecystokinin inhibitor (0.14 mg/hr of L364,718 [Merck Sharp & Dohme, West Point, PA] in dimethyl sulfoxide) into the arterial line during the 4-hour perfusion starting 15 minutes before time 0. Specimens for microscopy were obtained from all four preparations.

Results

Physiologic Injury Response

The control preparations (group I) remained normal in gross appearance throughout the 4-hour perfusion period. Weight gain was minimal and amylase activity in the perfusate remained within the normal range (Tables 1 and 2).

TABLE 1. *Weight Gain of the Preparations After 4 Hours of Perfusion in the Isolated* Ex Vivo *Perfused Canine Pancreas Preparation*

Group	n	Weight Gain (g)	p
I (controls)	4	10 ± 4	
II (FFA)	4	44 ± 12	<0.001*
VI (+ SOD + CAT)	4	20 ± 4	<0.005†
III (ISCH)	4	63 ± 29	<0.01*
VII (+ SOD + CAT)	4	22 ± 12	<0.05†
IV (POSS)	4	28 ± 7	<0.05*
VIII (+ SOD + CAT)	4	19 ± 6	<0.05†
V (CER)	4	31 ± 4	<0.001*
IX (+L364, 718)	4	9 ± 5	<0.001†

Mean ± SD. Student's t test.
* As compared to the control group (I).
† As compared to the respective untreated group.

TABLE 2. *Amylase Activity in the Perfusate After 4 Hours of Perfusion in the Isolated* Ex Vivo *Perfused Canine Pancreas Preparation*

Group	n	Amylase Activity (U/dL)	p
I (controls)	12	1200 ± 347	
II (FFA)	12	2781 ± 605	<0.001*
VI (+ SOD + CAT)	12	2075 ± 477	<0.05†
III (ISCH)	9	2923 ± 1180	<0.005*
VII (+ SOD + CAT)	4	2339 ± 164	0.05 < p < 0.1†
IV (POSS)	8	11601 ± 3328	<0.0001*
VIII (+ SOD + CAT)	4	4966 ± 3176	<0.005†
V (CER)	8	31686 ± 16089	<0.0001*
IX (+L364, 718)	4	9082 ± 5880	<0.02†

Mean ± SD. Student's t test.
* As compared to the control group (I).
† As compared to the respective untreated group.

Pancreatitis developed in the FFA, ISCH, POSS, and CER preparations (groups II to V). All became edematous, gained significant weight over the controls (Table 1), and the amylase activity in the perfusate increased significantly (Table 2).

Treatment of the FFA, ISCH, and POSS preparations with SOD and CAT (groups VI to VIII) and of the CER preparations with L364,718 (group IX) decreased the edema and significantly reduced weight gain (Table 1) and amylase activity (Table 2).

High-energy Phosphate Metabolism

The signal noise ratio was satisfactory in all experiments. Only trace levels of phosphocreatinine were observed when duodenal contamination was avoided. Figure 1 shows a typical phosphorus-31 spectrum.

In the control preparations (group I), the ATP and the P_i levels remained stable during the 4-hour perfusion period (Fig. 2). The initiation of injury with FFA infusion (group II) caused a decrease in the ATP levels and an increase in the P_i levels during the perfusion (Fig. 3). The β-ATP:PME ratio decreased to an average of 36% of baseline during the 4-hour perfusion ($p < 0.001$). Simultaneously the P_i:PME ratio increased to an average of 277% of baseline ($p < 0.05$) (Fig. 4). Treatment with SOD and CAT (group VI) significantly reduced the decline in the ATP levels, to 86% of baseline, but did not have significant effect on the P_i levels (Fig. 4).

In the ISCH preparations (group III), ATP decreased to undetectable levels 45 minutes after the induction of ischemia, with a concomitant increase in the P_i levels. Both the ATP and P_i levels returned to the preischemic levels and remained there during the 4-hour perfusion (Fig. 5). In the POSS and CER preparations (groups IV and V), no changes in the baseline ATP or P_i levels occurred during the 4-hour perfusion.

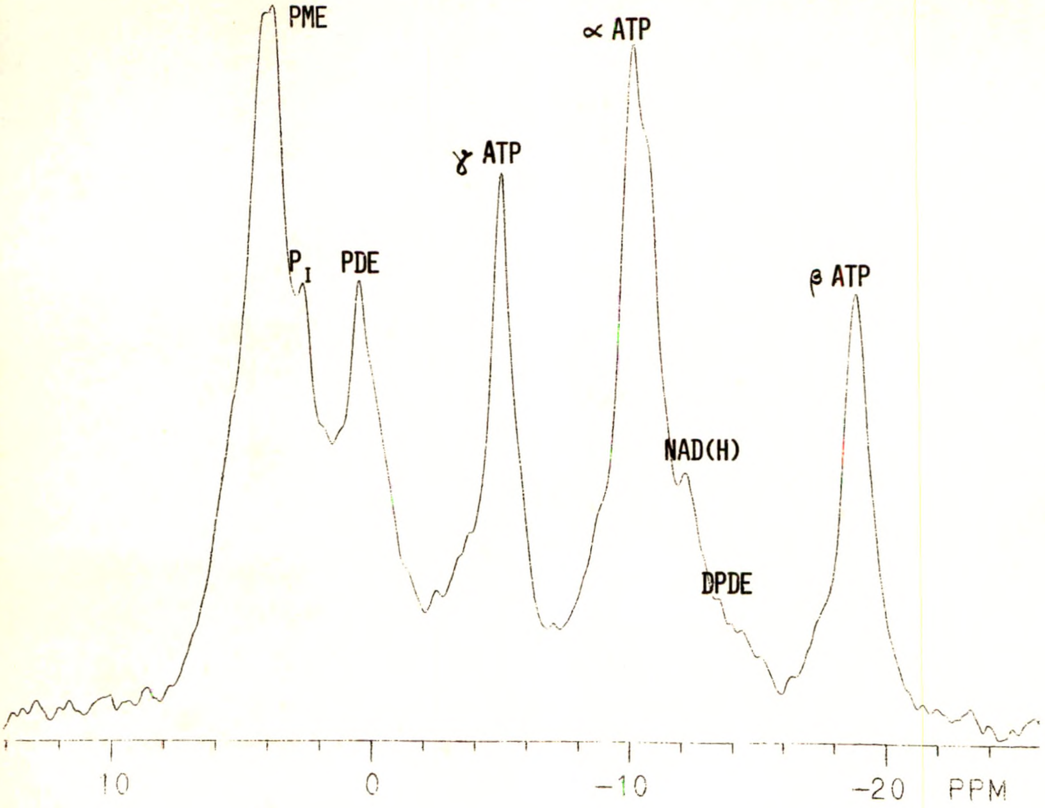


FIG. 1. A typical phosphorous-31 spectrum obtained from the control experiment with the isolated *ex vivo* perfused canine pancreas preparation. PME, phosphomonoesters; P_i, inorganic phosphate; PDE, phosphodiesters; ATP, adenosine triphosphates; NAD(H), nicotinamide adenine dinucleotide; DPDE, diphosphodiesters.

Cellular Structure

In the control preparations (group I), the cellular structure remained normal in both light and electron microscopic examinations throughout the 4-hour perfusion period. Acinar cells contained abundant zymogen granules at the apical portions of the cells (Fig. 6). Small condensing vacuoles also were noted. No alterations were noted in ductules, islets, or capillaries.

Both the FFA and ISCH preparations (groups II and

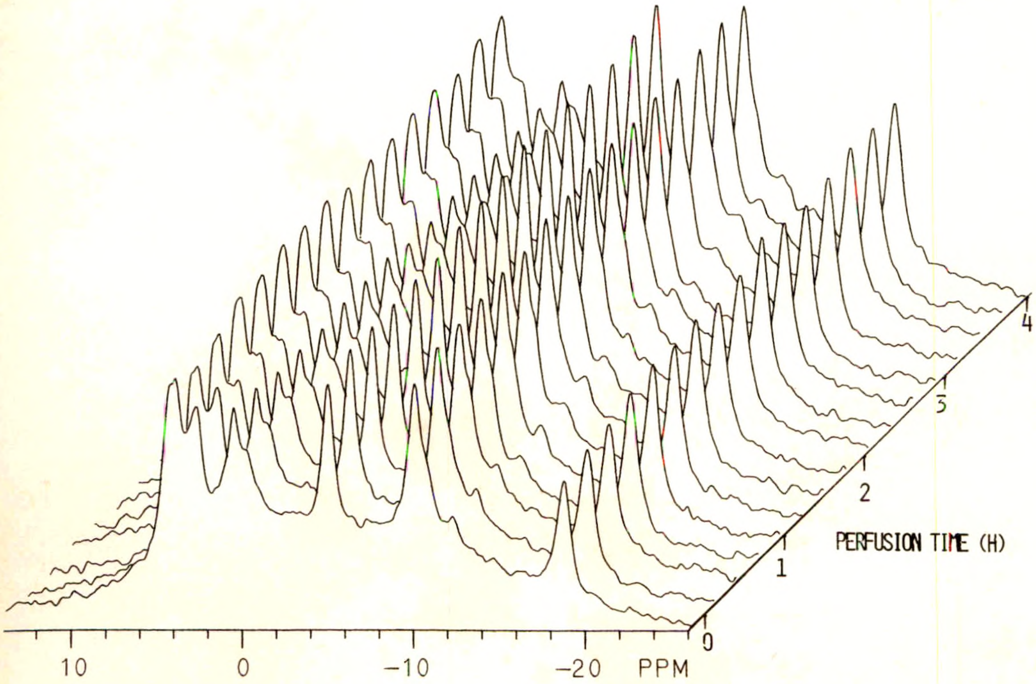


FIG. 2. Sequential phosphorous-31 spectra from a control preparation. No changes occurred during the 4-hour perfusion period.

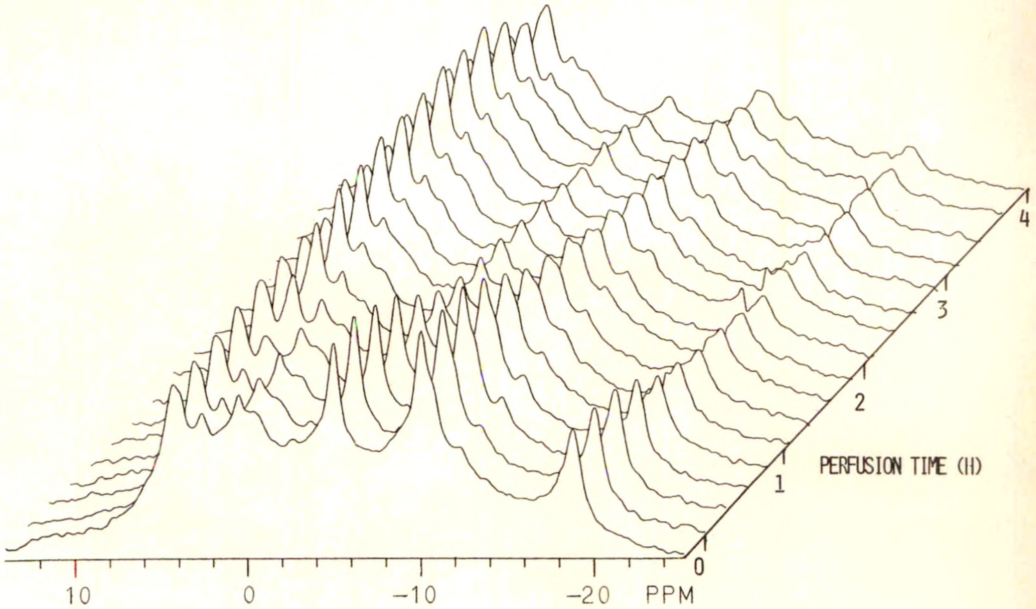


FIG. 3. Sequential phosphorous-31 spectra from an FFA preparation. Notice the decrease in ATP and the simultaneous increase in P_i during the 4-hour perfusion period.

III) were characterized by damage to capillaries accompanied by only minor changes in the acinar cells (decrease in zymogen granules). Endothelial cells were swollen. Frequent fibrin and platelet thrombi were identified (Figs. 7 and 8). These changes increased in severity from 1 hour to 4 hours of perfusion. Ductules and islets remained normal in both groups.

In the POSS and CER preparations (groups IV and V), striking changes occurred in the acinar cells with less severe alterations in capillaries. By light microscopy both preparations showed an increase in vacuoles accompanied by a decrease in zymogen granules. Groups IV and V (POSS, CER) could be differentiated easily from groups II and III (FFA, ISCH) with microscopic examination without knowledge of the experimental group. Electron microscopy demonstrated that many of the vacuoles in the POSS preparations represented dilatations of centroacinar lumens (Fig. 9). In addition there was an increase in condensing vacuoles as compared to control preparations. Sometimes there was conspicuous dilatation of cisternae of rough endoplasmic reticulum as well. These changes increased in severity during the 4-hour perfusion. The vacuoles seen by light microscopy in the CER preparations were demonstrated by electron microscopy to represent many enlarged condensing vacuoles (Fig. 10). The acinar cells also showed basolateral exocytosis in the CER preparations. In both POSS and CER preparations, mild swelling of endothelial cells sometimes was observed with some platelet thrombi. These vascular changes were less marked than those seen in the FFA and ISCH preparations (groups II and III). Ductules showed luminal dilatation in the POSS preparations but were normal in the CER preparations. Islets remained normal in both groups.

By light microscopy it was possible to differentiate qualitatively three of the four treated from the untreated preparations in the FFA, ISCH, and CER models by comparing and ranking histologic sections (Table 3). This separation was not possible between the treated (group VIII) and untreated POSS preparations (group IV) because in both groups the preparations had increased numbers of vacuoles by light microscopy reflecting the presence of duct obstruction, and centroacinar luminal dilatation.

By electron microscopy it was difficult to differentiate treated from untreated preparations after FFA, ISCH, and POSS stimuli because of the limited sample size available

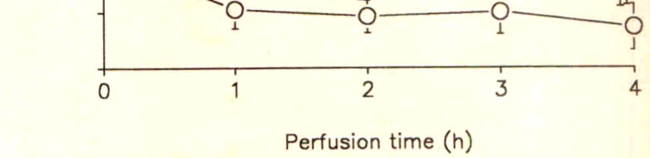


FIG. 4. The effect of superoxide dismutase (SOD) and catalase (CAT) on the acinar cell beta adenosine triphosphate:phosphomonoester (β-ATP:PME) and inorganic phosphate:phosphomonoester (P_i:PME) ratios in the FFA preparations. ○ change in β-ATP:PME ratio in the untreated FFA preparations. ● change in β-ATP:PME ratio in the SOD- and CAT-treated FFA preparations during 4-hour perfusion. △ change in P_i:PME ratio in the untreated FFA preparations during 4-hour perfusion. ▲ change in P_i:PME ratio in the SOD- and CAT-treated FFA preparations during 4-hour perfusion. Mean ± 95% confidence limit. Variance analysis. ns, no significant difference. *$p < 0.02$, **$p < 0.005$, ***$p < 0.001$.

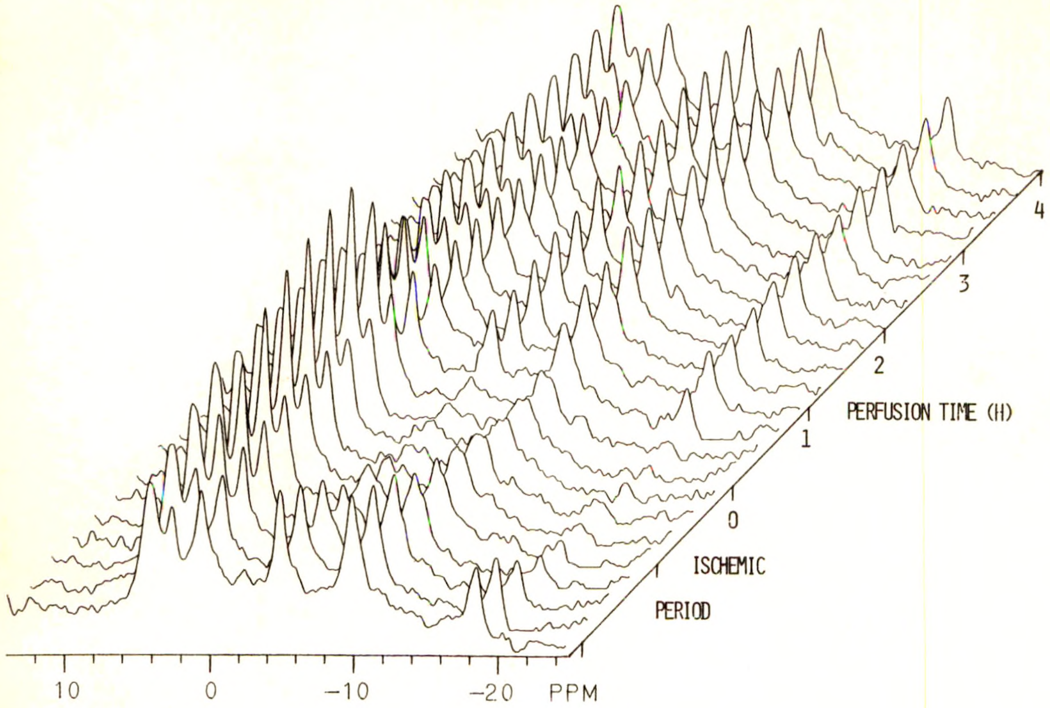


FIG. 5. Sequential phosphorous-31 spectra from an ISCH preparation. Notice the decrease in ATP and the simultaneous increase in P_i during the ischemia period, and the rapid recovery during the subsequent 4-hour perfusion period.

with that technique and the minor degree of acinar cell injury present in the FFA and ISCH preparations. Electron microscopic interpretation of the POSS preparations was complicated by the appearance of dilated centroacinar lumens reflecting the downstream duct obstruction. These lumens simulated the presence of condensing vacuoles and increased in number and size in both treated and untreated groups during the 4-hour perfusion period. In the CER preparations, treatment with L364,718 greatly reduced the number of condensing vacuoles and basolateral exocytosis. Furthermore zymogen granules were only slightly depleted. It was possible to differentiate the treated (group IX) from the untreated (group IV) preparations on the basis of qualitative changes at the ultrastructural level.

Discussion

Many experimental models have been developed to study the pathophysiology of acute pancreatitis. Among the many stimuli used to initiate pancreatitis have been duodenal obstruction, bile injection into the pancreatic duct, and cerulein administration.[7] The physiologic injury response in all models has been similar: edema formation, hyperamylasemia, and in severe pancreatitis, hemorrhage and necrosis. Most studies have focused on monitoring these physiologic injury responses taking place in the animal after the injury. Many of the models have no clinical counterparts.

In our effort to develop a model that would simulate pancreatitis as seen in the human and allow study of the early pathogenetic steps taking place in the pancreas, the isolated canine pancreas preparation was adopted[8] and modified.[1] Models of pancreatitis simulating that seen clinically with hyperlipemia, gallstones, and with ischemia were developed and studied extensively. It was demonstrated that the usual physiologic injury response (edema, weight gain, and hyperamylasemia) took place after each of the stimuli.[1–3] Furthermore it was demonstrated that the first measurable injury was an increase in capillary permeability[9] mediated by the release of oxygen-derived free radicals.[5] Subsequent studies demonstrated that the

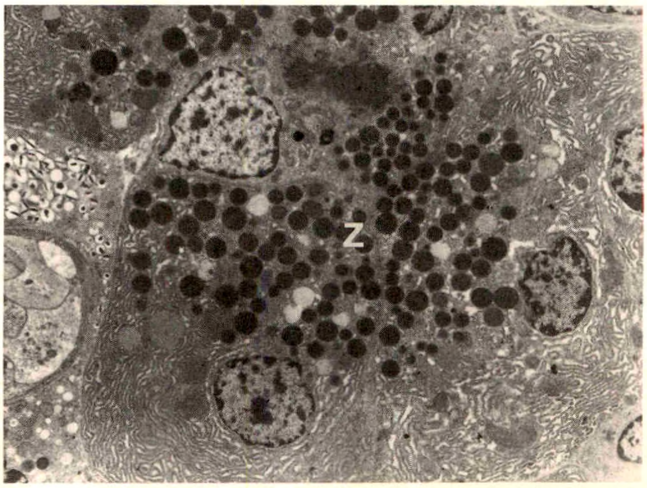
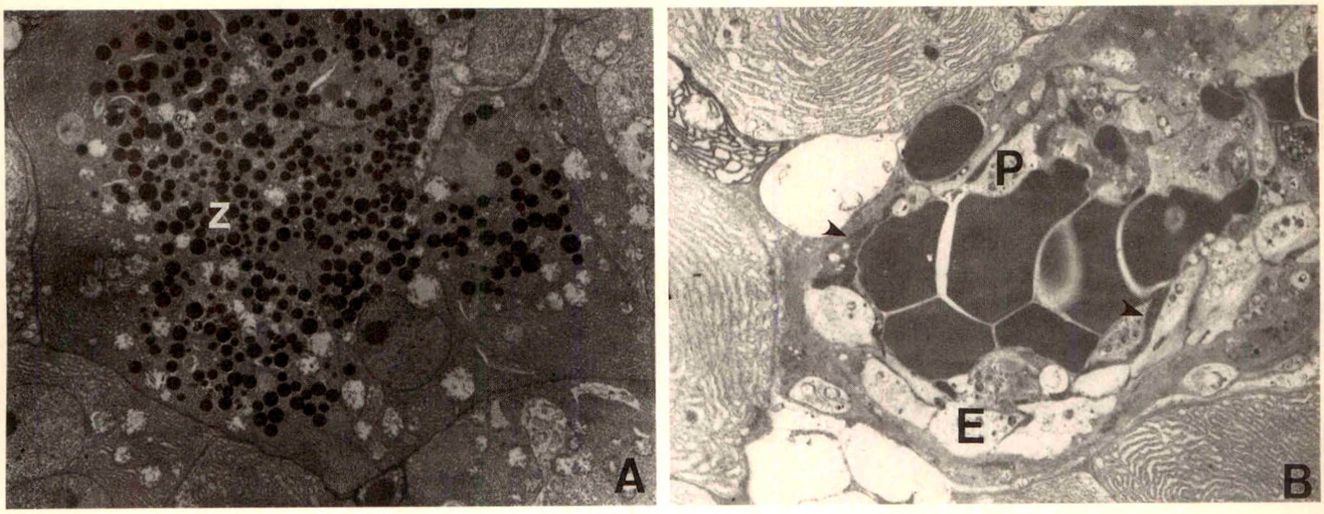


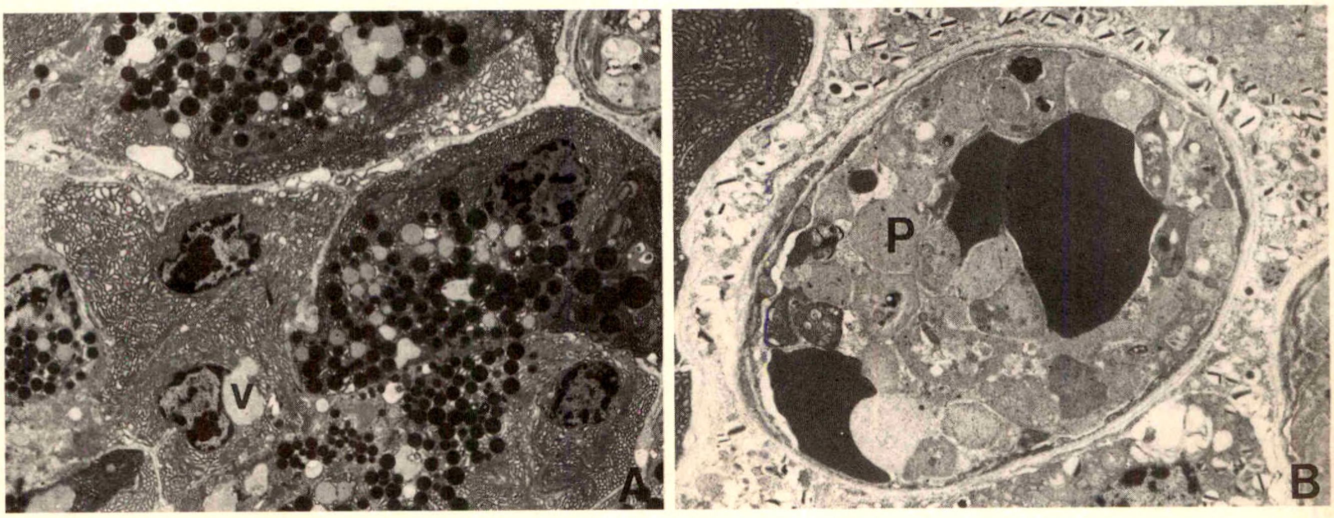
FIG. 6. Electron micrograph of a control preparation after 4-hour perfusion showing normal complement of zymogen (Z) granules and lack of large vacuoles (uranyl acetate and lead citrate, ×3200).



FIGS. 7A and B. Electron micrographs of an FFA preparation after 4-hour perfusion. (A) Relative preservation of acinar cell structure with mild decrease in zymogen granules (Z). (B) Capillary, which showed swollen endothelial cells (E) with platelets (P) and fibrin strands (arrowheads) in lumen (uranyl acetate and lead citrate, (A) ×1800, (B) ×3600).

free radicals were generated by the enzyme xanthine oxidase.[10] Most recently a fourth model of pancreatitis, using supramaximal stimulatory doses of cerulein, was adapted to the canine isolated *ex vivo* perfused pancreas preparation.[4] This model lacks an obvious clinical counterpart. Although the physiologic injury response is similar to that seen in the other three models (FFA, ISCH, and POSS), the injury is not mediated by oxygen-derived free radicals but rather by cholecystokin receptors on the acinar cells.[4,6] Until now the vast majority of studies of experimental pancreatitis, including ours, monitored changes taking place at the organ level. These studies all recorded similar physiologic responses, independent of the initiating stimulus. In an effort to study early biochemical and morphologic changes taking place in acute pancreatitis on cellular and subcellular levels, the present experiments were performed.

High-energy phosphate metabolism was monitored by placing our preparation in the bore of the magnet connected to a spectrometer and following phosphorus-31 spectra. Because it is noninvasive, this method does not disturb the experiment under study and it allows continuous monitoring of the preparation during the perfusion. In the control preparations levels of ATP and its degradation product P_i remained stable throughout the perfusion. Unlike the physiologic injury response, which was



FIGS. 8A and B. Electron micrographs of an ISCH preparation after 4-hour perfusion. (A) Relative preservation of acinar cell structure with occasional small vacuoles (V). (B) Capillary containing platelet thrombus (uranyl acetate and lead citrate, (A) ×2600, (B) ×4300).

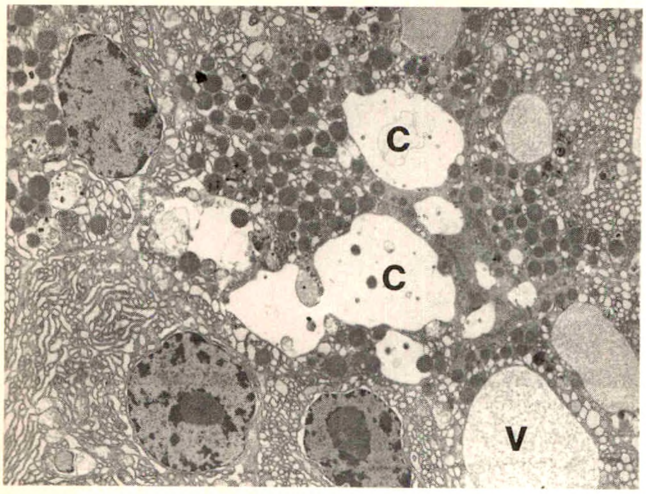


FIG. 9. Electron micrograph of a POSS preparation after 4-hour perfusion showing dilatation of centroacinar lumen (C) simulating vacuoles. True vacuoles (V) contain flocculent material and do not show microvilli (uranyl acetate and lead citrate, ×2900).

similar in all four models of pancreatitis, ATP metabolism differed markedly from model to model. In the FFA preparations, ATP levels decreased significantly and stayed depressed during the entire perfusion. However, in the ISCH preparations, ATP levels decreased only during the period of ischemia, but then returned to normal baseline levels during the 4-hour perfusion when the physiologic injury response of pancreatitis was evolving. In the POSS and CER preparations, ATP levels remained normal throughout the perfusion period, despite of the evolution of the physiologic injury response of pancreatitis. A previous study performed by another group demonstrated a decrease in ATP levels by biochemical methods after the induction of pancreatitis by injecting a fresh trypsin, bile, and blood mixture in the pancreatic duct of the dog.[11] Another study of pancreatitis initiated in the rat by an intraparenchymal injection of sodium taurocholate also demonstrated a significant decrease in ATP levels by phosphorus-31 MRS.[12] The present study demonstrates that a change in ATP metabolism depends on the model used. The fact that acute pancreatitis can develop in two of our four models of pancreatitis (POSS and CER) without any disturbance in ATP metabolism suggests that alterations in high-energy phosphate metabolism are not essential steps in the pathogenesis of all forms of pancreatitis.

The morphologic changes seen in the acinar cells by light and electron microscopy also were not similar in all four models. The variety of the morphologic changes help, in part, to explain the different patterns seen in ATP metabolism. In the FFA preparations the morphologic changes were confined primarily to the capillaries, with edematous endothelium with platelet and fibrin thrombi. There were only minimal changes in the acinar cells. This suggests that the earliest injury in this model is to the small vessels and could explain the ATP decrease on the basis of ischemia. In the ISCH preparations, the morphologic changes were similar to those in the FFA preparations, with the most severe injury seen in the capillaries and well-preserved acinar cells. It is not surprising that ATP levels decrease during the period of ischemia. It is more difficult to explain the return to normal of ATP levels during perfusion, in view of the capillary injury identified.

The morphologic changes seen in the CER preparations were markedly different from those seen in the FFA and ISCH preparations, but identical to those seen in the intact animal preparations in which pancreatitis is initiated by a supramaximal stimulatory dose of cerulein.[13] Zymogen depletion, large condensing vacuole formation, and basolateral exocytosis occurred. Capillary injury was minimal. The morphologic changes seen in the POSS preparations were similar, but in addition, progressive dilatation of the centroacinar lumens was seen, reflecting the downstream obstruction. It is interesting, and unexpected, to learn that the physiologic injury response of acute pancreatitis can develop in these two models (CER, POSS), with marked changes in subcellular morphology, without disturbance of ATP metabolism. This suggests that acute pancreatitis can develop, at least during its earliest stage, without disturbing important cellular metabolic activities.

The biochemical and morphologic changes observed in these four models can be ameliorated, at least in part, by treatment with free radical scavengers or a cholecystokinin inhibitor. Just as the physiologic changes in the FFA preparations were ameliorated, so were the biochemical and morphologic changes when SOD and CAT were added to the perfusate. In addition the morphologic

TABLE 3. *Effect of Treatment with SOD and CAT of the FFA, ISCH, and POSS Preparations, and with L364,718 of the CER Preparations, on the Morphology of the Preparations*

Severity of Injury (rank)	FFA	ISCH	POSS	CER
1	Untreated	Untreated	Untreated	Untreated
2	Untreated	Untreated	Treated	Untreated
3	Untreated	Untreated	Untreated	Treated
4	Treated	Treated	Treated	Untreated
5	Treated	Untreated	Treated	Untreated
6	Treated	Treated	Treated	Treated
7	Untreated	Treated	Untreated	Treated
8		Treated	Untreated	Treated

Light microscopy slides were ranked with regard to acinar cell injury within each model of pancreatitis without knowledge of treatment group. A rank of 1 was applied to the preparation with the most severe changes to a rank of 8 for the preparation with the least severe alterations. Criteria indicating more severe acinar cell injury included increasing numbers of vacuoles and decreasing amount of zymogen.

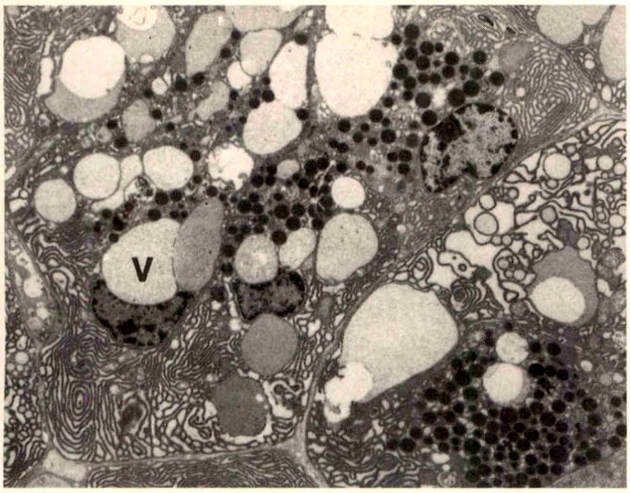


FIG. 10. Electron micrograph of a CER preparation after 4-hour perfusion showing depletion of zymogen granules (Z) and accumulation of many large vacuoles (V) (uranyl acetate and lead citrate, ×2300).

changes seen in the ISCH and CER preparations were modified by pretreatment with SOD and CAT, or a cholecystokinin inhibitor, respectively. Any amelioration of the morphologic changes in the POSS preparations by SOD and CAT pretreatment were obscured by the progressive dilatation of centroacinar lumens that took place secondary to the downstream duct obstruction during the 4-hour perfusion. These findings suggest that, similar to the physiologic injury response, the changes in high-energy phosphate metabolism and in cellular structure are mediated, at least in part, by oxygen-derived free radicals in the FFA and ISCH models, and by the cholecystokinin receptor in the CER model.

Previous studies from many laboratories, including ours, demonstrated that acute pancreatitis is a relatively homogenous disorder, with the pancreas reacting in a rather standard fashion, no matter how disparate the injurious stimulus. These data come primarily from models studying organ physiology. The current experiments suggest that there might be significant differences between pancreatitis initiated by one stimulus, as compared to another, on the subcellular level. Thus it would seem to be very important to study several models of acute pancreatitis to avoid the risk of idiosyncrasies when studying just one model. More importantly, however, our results suggest that even though clinically acute pancreatitis might appear identical, independent of the initiating stimulus (most often alcohol or passage of a gallstone), in terms of cellular events the diseases might be different depending on the etiology. This suggests that all clinical types of pancreatitis might not respond to the same treatment regimens. Currently the treatment of acute pancreatitis is symptomatic. There are no treatment modalities that have been demonstrated to be effective in modifying the clinical course. For effective therapy to be developed, more information is needed concerning the pathogenesis of the disease in each etiologic subgroup.

Acknowledgment

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Experimental Obliterative Cholangitis

A Model for the Study of Biliary Atresia

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Noninfectious obliterative cholangitis results from biliary tract inflammation in clinical conditions such as biliary atresia and sclerosing cholangitis. The purpose of this study was to develop an animal model of noninfectious biliary tract inflammation and fibrosis. An implantable osmotic pump was connected to a catheter placed into the gallbladder of hamsters. Phorbol myristate acetate (PMA) was infused into the biliary tract for periods of 6 hours to 28 days. After 7 days the animals developed neutrophil infiltration, cellular necrosis, and edema of the biliary ducts. After 14 days, the animals demonstrated intrahepatic cholestasis with bile duct fibrosis and acute and chronic inflammatory cell infiltration. By 28 days pronounced portal fibrosis was present, some of which created an early bridging cirrhosis pattern. In addition there was evidence of neocholangiogenesis. We conclude that long-term PMA infusion into the biliary tract generates an inflammatory response characterized by obliterative cholangitis and fibrosis, sharing many of the histologic features of human biliary atresia. This model may provide a relatively simple technique for investigating the process of nonpyogenic biliary tract inflammation.

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BILIARY ATRESIA WAS formerly considered an accident in embryogenesis which resulted in nonpatency of the extrahepatic biliary tree. However, more recent evidence suggests that this is not the case.[1] Clinical evidence of obstructive jaundice usually is not present at birth but typically appears at several weeks of age. In addition Kasai et al.[2,3] provided clinical and histopathologic evidence that patent bile ducts are present in the first 2 months of life but gradually disappear, so that after 4 months of age only fibrous, nonpatent ducts remain. Further evidence against an embryonic pathogenesis for biliary atresia is provided by the observation that it is ordinarily not associated with congenital anomalies of other major systems, one of the characteristic features of discrete teratogenic events.[4] Last biliary atresia is an exceedingly uncommon finding at autopsy of aborted fetuses or neonates, suggesting a postnatal disease process.[5]

A variety of other explanations for this condition have been offered, including malunion of the pancreatic and biliary ductal systems,[6] fetal vascular accidents,[7-9] and perhaps most convincingly, viral infections.[10-12] In 1977 Bill et al.[5] pointed out the prominent inflammatory response associated with biliary atresia and proposed that the disease might result from a dynamic, acquired inflammatory process. Subsequently other investigators implicated the Reovirus type III as a potential pathogen. Experimental studies in mice and epidemiologic data from human studies provided support for this concept.[10-12] The concept also was developed that biliary atresia results not necessarily from a specific pathogen but rather from a nonspecific activation of the endogenous inflammatory system. The mechanisms by which the liver and biliary tree of the neonate become targeted, and the specific pathogenic mediators involved, are unknown.

The purpose of this investigation was to evaluate the hypothesis that the initiation of acute inflammation in the biliary tract with a nonspecific trigger such as phorbol myristate acetate (PMA) would result in chronic inflammation, fibrosis, and obliteration of the bile ducts. These histologic changes are characteristic of chronic nonpyogenic inflammation of the biliary ducts in humans; in children the common process with these characteristics is biliary atresia; in adults sclerosing cholangitis is the notable example. The study suggests that inflammation and fibrosis involving the bile ducts can be induced with PMA and that the histologic features of this injury resemble those seen in humans with biliary atresia and other in-

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flammatory biliary processes. In addition the known relationship of PMA as a potent stimulator of oxygen radical production by stimulated phagocytic cells suggests that there may be a relationship between this type of biliary inflammation and oxygen radical-mediated tissue injury.

Materials and Methods

Implantable mini-osmotic pumps (Alza Corp., Palo Alto, CA) were prepared with either normal saline or PMA in saline (Sigma Chemical Co., St. Louis, MO). Pumps varied in size and capacity to deliver the infusate at a constant rate (model 2001-250 μL at 0.46 μL/hr for 7 days; model 2002-250 μL at 1.03 μL/hr for 14 days; model 2ML-2200 μL at 2.69 μL/hr for 28 days) during a predetermined time period for 7 to 28 days. Animals in the 6-hour study group were given a single injection of PMA or saline. All infusions were through a polyethylene catheter (PE 60) placed surgically into the gallbladder. The dose of PMA in all study groups was 25 μg/kg/day. In each case the pump and tubing were primed before implantation.

Experimental protocols were approved by the University of Michigan Committee on Use and Care of Animals. Male Syrian golden hamsters weighing 80 g (Charles River Laboratories, Wilmington, MA) were anesthetized with ketamine hydrochloride (50 mg/kg intramuscularly). Using aseptic techniques the liver and gallbladder were exposed through a right subcostal incision. A 6-0 silk purse string was placed in the fundus of the gallbladder. A subcutaneous pocket then was created in the right flank, the pump inserted, and the polyethylene tubing tunneled through the abdominal wall. The polyethylene tubing then was placed into the fundus of the gallbladder and secured. The abdomen was irrigated with sterile saline, closed, and the animals were returned to standardized housing with rodent chow and water available *ad libitum.*

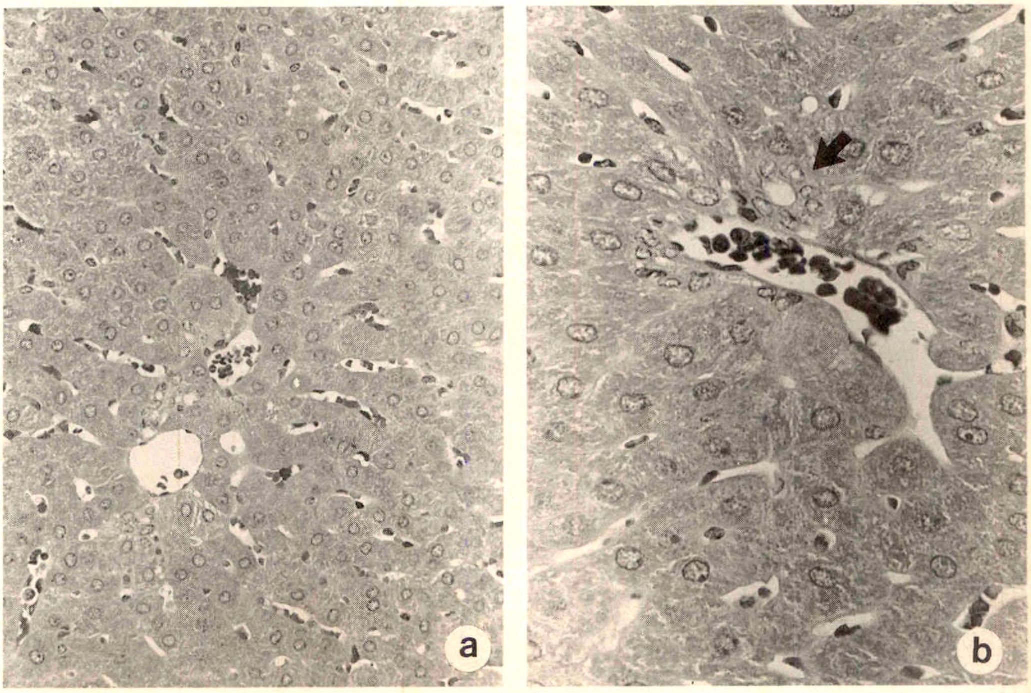
Animals were divided randomly into groups of five each according to the time of PMA or saline infusion. Study groups were prepared with infusions lasting 6 hours, 7, 14, or 28 days with PMA or saline.

At the designated time that the animals were killed, the animals were anesthetized with ketamine as before and their subcostal incisions were re-entered. The liver, gallbladder, and pancreas were resected *en bloc* and preserved in formaldehyde. Routine processing for histologic examination was accomplished and tissues were stained with hematoxylin and eosin as well as trichrome elastic stains. Slides were examined randomly by a pathologist blinded as to treatment.

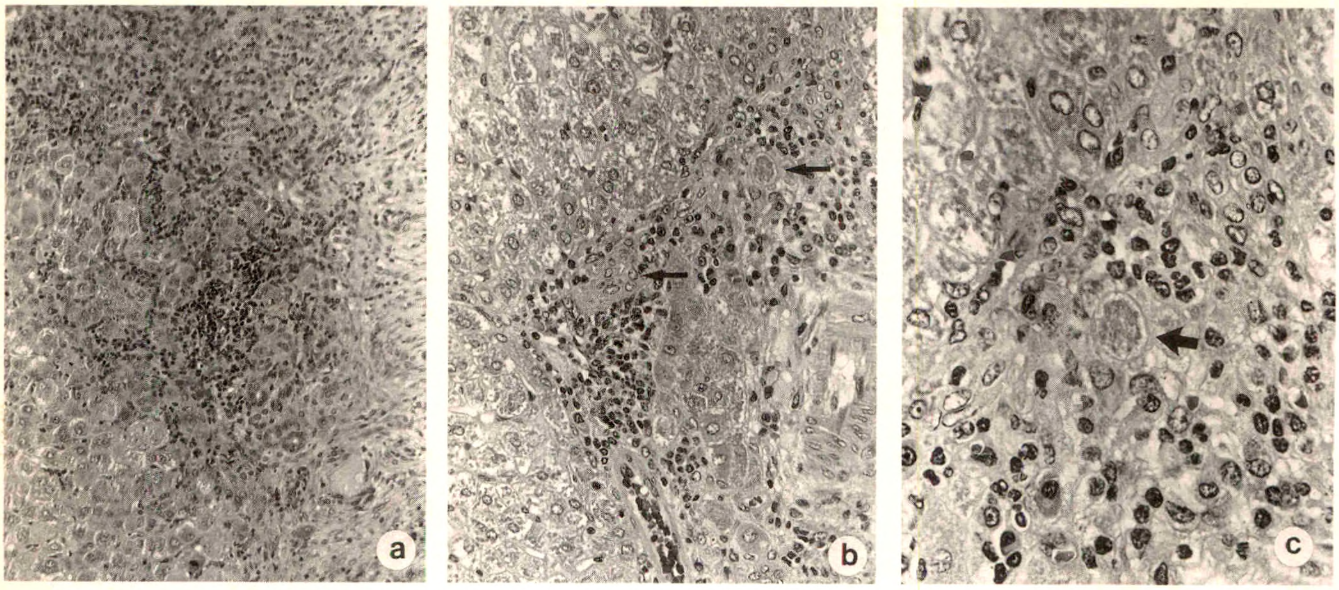
Results

Saline-infused animals demonstrated normal hepatic and biliary architecture at all times. Figure 1 illustrates the liver of an animal infused for 28 days with saline. There is no evidence of periportal inflammation or fibrosis.

In contrast to the animals infused with saline, those infused with PMA developed striking periductal inflammatory alterations. A single injection of PMA resulted in significant acute periductal inflammation in the liver with



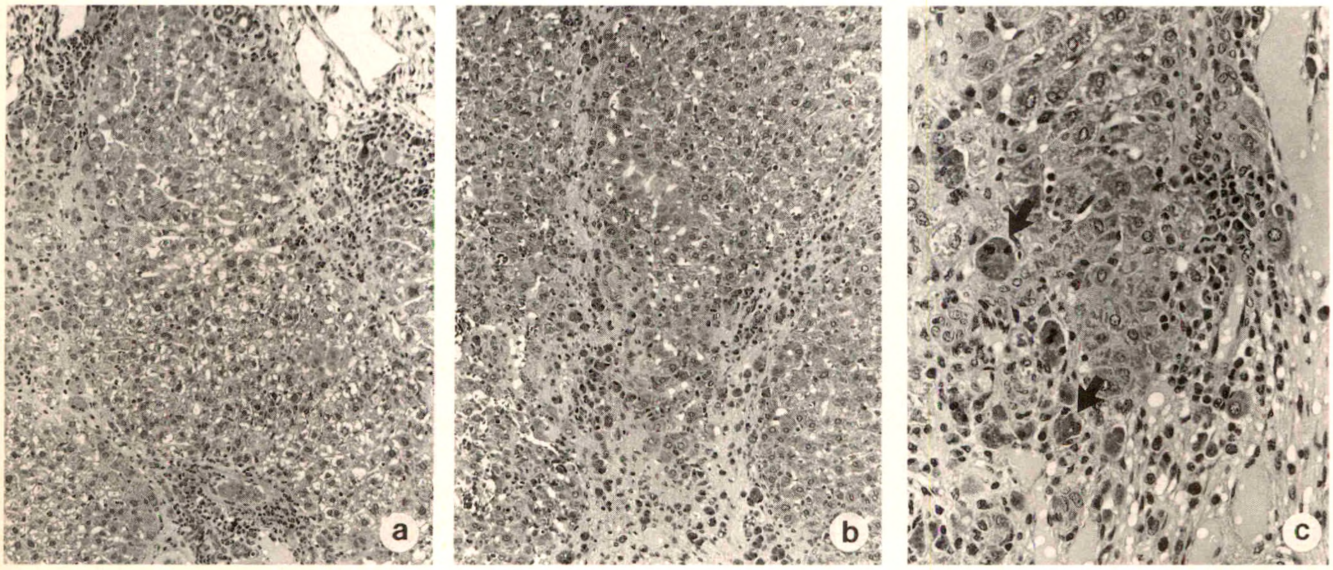
FIGS. 1a and b. Histologic appearance of the liver of a control animal given a saline infusion for 28 days. (a) A low-power view of a hepatic lobule illustrates no abnormality. (b) A high-power view of a normal portal triad is shown, including a bile duct as pointed out by the arrow (hematoxylin and eosin stain; a, 200×; b, 400×).



FIGS. 2a–c. Histologic alterations in the liver of animals given PMA infusion for 7 days. There is an intense periportal inflammatory infiltrate with extension into surrounding hepacytes, as illustrated in a. This inflammatory infiltrate was associated with destruction of bile ducts, as illustrated in b (arrows). Cholestasis was also present with a bile plug in a destroyed bile duct illustrated in c (arrow) (hematoxylin and eosin stain; a, 100×; b, 200×; and c, 400×).

neutrophilic infiltrates, edema, and some patchy necrosis of the bile ducts. After 7 days of PMA infusion, more severe inflammatory changes were present. As illustrated in Figure 2, pronounced inflammatory infiltrates were present in the livers of these animals. These infiltrates were primarily periductal but also extended into the surrounding liver parenchyma. At this time the inflammatory infiltrate was primarily acute in nature with a predominance of neutrophils, but chronic inflammatory cells such as macrophages, lymphocytes, and plasma cells were also present. The inflammatory infiltrate was associated with destruction of the bile ducts and focal hepatocyte necrosis was also evident. Prominent cholestasis was present within hepatocytes as well as in the bile ducts.

In animals infused with PMA for 14 days, a progression of the inflammatory response was seen with early fibrosis as well on ongoing inflammation and necrosis. This is illustrated in Figure 3. At this time a mixed acute and



FIGS. 3a–c. Histologic alterations in the liver of animals given PMA infusions for 14 days. There was ongoing intense periportal inflammation with the destruction of bile ducts, as illustrated in a. Early fibrosis was present in the portal regions (Figure 3B) and prominent cholestasis was present (c, arrows) (hematoxylin and eosin stain; a, 100×; b, 200×; and c, 400×).

chronic inflammatory infiltrate was present with a majority of the inflammatory cells consisting of lymphocytes, macrophages, and plasma cells. Despite the predominant chronic inflammatory infiltrate, ongoing tissue injury was present with destruction of the bile ducts and patchy hepatocyte necrosis. Prominent cholestasis was present in some of the hepatocytes and bile ducts. Early fibrosis was present, including some delicate bridging scarring of the liver parenchyma, indicative of early cirrhosis.

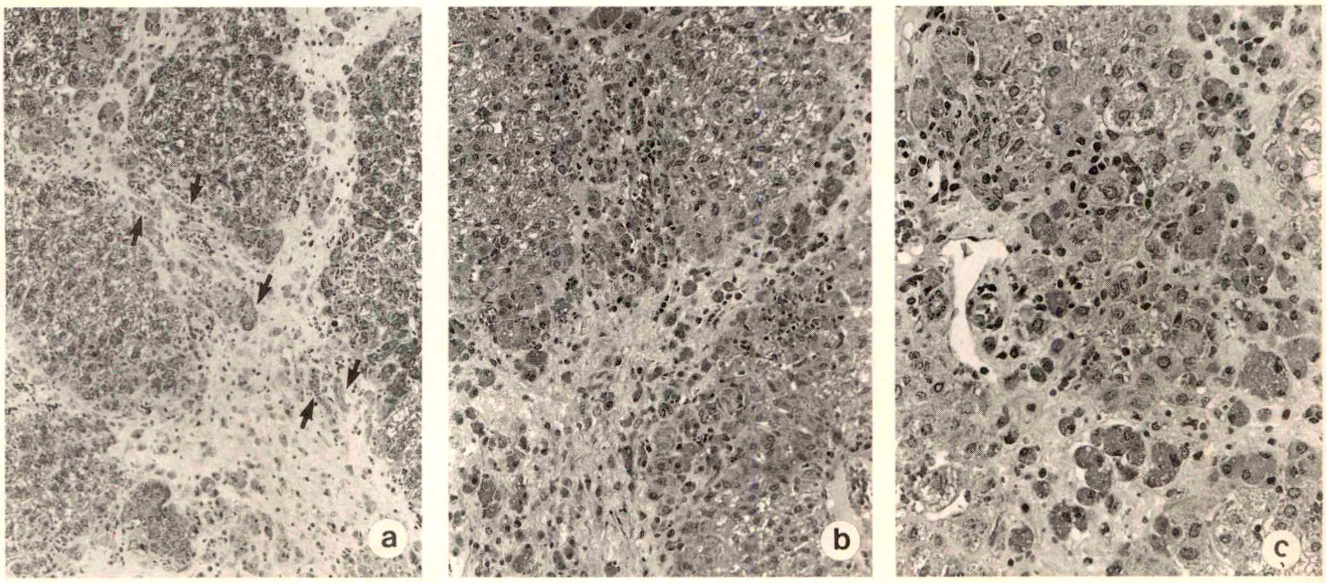
After 28 days of PMA infusion, the primary histologic appearance of the liver was that of scarring and early cirrhosis. As shown in Figure 4, bands of collagen separate lobules of hepatocytes creating the characteristic appearance of micronodular cirrhosis. Some inflammation per- that it is ordinarily not associated with congenital anomalies of other major systems, one of the characteristic features of discrete teratogenic events.[4] Last biliary atresia is an exceedingly uncommon finding at autopsy of aborted fetuses or neonates, suggesting a postnatal disease process.[5]

The above histologic alterations seen with PMA infusion are similar to those described in patients with noninfectious cholangitis secondary to biliary atresia or sclerosing cholangitis. This is illustrated in Figure 5, which represents varying stages of the histologic abnormalities present in liver biopsies from patients with biliary atresia. Figure 5A shows prominent periductal inflammation with destruction of bile ducts that occurs primarily early in the course of the disease. Figure 5B shows a liver biopsy from a child with long-standing jaundice secondary to biliary atresia. Prominent periportal fibrosis is present along with disordered bile duct epithelial proliferation (neocholangiogenesis). Some chronic inflammatory cells are present, but the primary histologic diagnosis is that of early micronodular cirrhosis. Thus the characteristic morphologic alterations seen in patients with biliary atresia are reproduced in this experimental model.

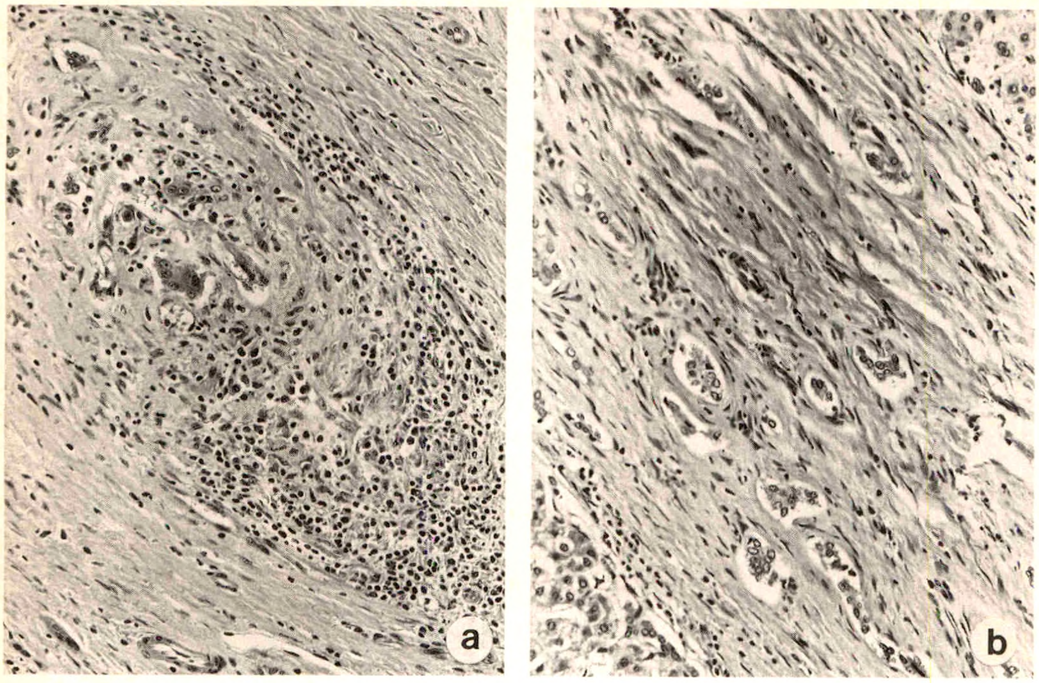
Discussion

Biliary atresia occurs with an estimated frequency of 1 in 15,000 to 25,000 neonates.[13,14] The histopathology typically includes extrahepatic bile duct fibrosis with intrahepatic bile duct proliferation. Inflammatory cells (both neutrophils and macrophages) are characteristic in both locations and ultimately cirrhosis may develop. Patients afflicted with biliary atresia continue to suffer predictable morbidity and mortality despite surgical advances such as the portoenterostomy procedures and liver transplantation. Unfortunately the pathogenic mechanisms involved in the evolution of this condition are understood poorly. Current evidence suggests that this condition is the result of an acquired inflammatory process that preferentially targets the neonatal biliary tract.[1] A variety of nonspecific initiating events, possibly including neonatal Reovirus type III infection, may trigger this process.[10–12]

This study was designed to develop a model for the study of biliary tract inflammatory processes such as this. It is well recognized that neutrophils and other inflammatory effector cells may participate in the generation of host tissue injury in a variety of experimental and clinical situations.[15–18] Phorbol myristate acetate is a synthetic phorbol ester known to activate phagocytic cells[19–21] as



FIGS. 4a–c. Histologic alterations in the liver of animals given PMA infusions for 28 days. At the time fibrosis was prominent with the development of cirrhosis. In addition there was disordered proliferation of bile duct epithelium (neocholangiogenesis) (a, arrows). Some ongoing chronic inflammation was present, but it was less intense than at the early time points and prominent cholestasis was present (b and c) (hematoxylin and eosin stain; a, 100×; b, 200×, and c, 400×).



FIGS. 5a and b. Comparative histologic alterations in patients with biliary atresia. In the early stages of the disease, there is prominent periportal inflammation with destruction of the bile ducts (a). In the chronic stages of the disease, fibrosis predominates with dense bands of collagen, micronodular cirrhosis, and disordered bile duct proliferation (neocholangiogenesis), as illustrated in b (hematoxylin and eosin stain, 200×).

well as endothelial cells *in vitro*.[22] This process is the result of the activation of protein kinase C, a proximal and therefore nonspecific step in the process of signal transduction in phagocytic cells. In particular PMA induces the oxidative burst in phagocytic cells and in fact, often serves as the laboratory standard to provide maximally activated phagocytic cells. Phorbol myristate acetate-stimulated neutrophils have been implicated in experimental models of inflammatory pulmonary injury.[23-26] Importantly PMA itself is not toxic in neutrophil-depleted experimental systems,[23] in systems where neutrophil adherence to endothelial cells is prevented,[26] or in the presence of neutrophils derived from patients with chronic granulomatous disease (CGD) in whom granulocytes are intrinsically incapable of generating oxygen radicals.[23] Thus it appears that PMA itself is not toxic, but that when administered in the presence of normally functioning neutrophils, injury results.

Reactive oxygen products are widely implicated in a variety of pathologic processes mediated by the endogenous inflammatory response. These products include the superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), the hydroxyl radical ($^{\bullet}OH$), and other reactive intermediates generated during the oxidative burst by phagocytic cells activated by PMA. For this reason PMA was selected to induce the biliary inflammatory process in this study. It appears that the resultant tissue injury in this model is associated with an acute and chronic inflammatory process leading to fibrosis of portions of the biliary tree. The histologic features of this injury are similar to those of biliary atresia.

This is a relatively straightforward and inexpensive model that may be useful in the study of pathogenic mechanisms of biliary atresia and other nonpyogenic biliary inflammatory processes. The association of PMA with neutrophil and other phagocytic cell oxidant production suggests that oxidant-mediated tissue injury may play a role in the pathogenesis of this type of biliary inflammation.

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Aortic Dissection with the Entrance Tear in the Descending Thoracic Aorta

Analysis of 40 Necropsy Patients

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Clinical and necropsy findings are described in 40 patients who had aortic dissection with the entrance tear in the descending thoracic aorta. Their ages at death ranged from 39 to 91 years (mean, 66 years); 24 (60%) were men and 16 (40%) were women. Systemic hypertension was present by history in 33 patients (83%) and the hearts were of increased weight in 78%. Of the 40 patients, 31 (78%) had no operative intervention, while 9 (22%) underwent operation for aortic dissection. Of the 31 patients without operative therapy, the diagnosis of aortic dissection was established in life in 9 patients (29%) and at necropsy in 22 (71%). The interval from aortic dissection to death was 30 days or less in 13 patients (42%); rupture of the false channel was the cause of death in 9 patients (69%), renal failure in 2 (15%), and the cause was unclear in 2 (15%). The interval from aortic dissection to death was more than 30 days in 18 (58%) of the 31 patients without operative therapy. The cause of death in these 18 patients was related to the dissection in 11 (61%) (rupture of the false channel in 5; renal failure from dissection in 3, and rupture of the false channel of a second acute dissection in 3), but in the other 7 patients (39%) death was unrelated to the dissection but a nonfatal complication, specifically stenosis of the true channel from compression by a thrombus-filled false channel, occurred in 4 of these 7 patients. Thus only 3 (10%) of the 31 patients without operative therapy had no complications of aortic dissection. All nine patients who underwent operation had had an aortic dissection within 30 days, and the operation was performed because of a major complication of the dissection. Four patients survived 8 to 84 months after the operation. Thus early operative intervention (before the appearance of complications) appears justified in patients with aortic dissection with the entrance tear in the descending thoracic aorta to prevent rupture of the false channel acutely or after initial healing; to prevent renal failure from compression of renal arteries by an aneurysmal false channel; to prevent true channel stenosis from compression by a thrombus-filled false channel; and possibly to prevent the recurrence of acute dissection.

DURING THE PAST 30 years, 182 patients with spontaneous (noniatrogenic) aortic dissection were studied at necropsy in the Pathology Branch, National Heart, Lung, and Blood Institute. The entrance tear was located in the ascending aorta in 128 patients (70%), transverse aorta in 12 patients (7%), descending thoracic aorta in 40 patients (22%), and abdominal aorta in 2 patients (1%). This report describes certain clinical and necropsy findings in the 40 patients in whom the entrance tear was located in the descending thoracic aorta and discusses therapeutic implications of the findings.

Methods

The necropsy records of the Pathology Branch, National Heart, Lung, and Blood Institute from 1959 to April 1990 were searched for cases coded as 'aortic dissection.' A total of 194 cases were so coded. Twelve were excluded because of an iatrogenic etiology—the aortic entrance tear was adjacent to an aortotomy. All 142 cases with the entrance tear in either ascending, transverse, or abdominal aorta also were excluded from this analysis. The remaining 40 cases had the entrance tear in the descending thoracic aorta and they constitute the study group.

The hearts and aortas in all 40 patients originally were examined and classified by W. C. Roberts; 26 of the 40 cases were examined by C. S. Roberts and re-examined by W. C. Roberts. Of the 14 cases not re-examined, photographs of the aortas were available for examination in seven. Of the 40 patients, 1 was studied at necropsy in 1968, 20 were studied from 1971 to 1980, and 19 from 1981 to 1990. The 40 cases were submitted from 11 different hospitals: 38 cases from local and 2 cases from nonlocal hospitals. Of the 40 cases, 1 hospital submitted 11 cases; 1 hospital, 8 cases; 2 hospitals, 4 cases each; 2 hospitals, 3 cases each; 3 hospitals, 2 cases each; and 3

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TABLE 1. *Clinical and Morphologic Observations in 31 Necropsy Patients with Aortic Dissection with the Entrance Tear in Descending Thoracic Aorta*

Patient Number	Age at Death (Years)	Sex	SH	Aorto-gram	AD Diagnosed Clinically	Interval AD to Death	Mode of Death			Aortic Dissection		Dissection in Abdominal Aorta	FC Thrombus	FC Rupture	TC Stenosis	Reentry Tear	AAA	HW (g)	LV Fibrosis
							AR	RF	Other	A	H								
1	40	F	+	0	0	7d	+	0	0	+	0	+(a)	+	+	0	0	0	—	0
2	49	F	+	0	+	30d	+	0	0	+	0	0	+	+	0	0	0	360	0
3	57	M	+	0	0	1d	+	0	0	+	0	++	+	+	0	0	0	360	0
4	58	M	+	0	0	9d	+	0	0	+	0	0	++	+	+(b)	0	0	810	0
5	60	M	0	0	0	4d	+	0	0	+	0	+	+	+	0	0	0	340	0
6	63	F	+	0	0	7d	0	0	U	+	0	0(c)	+	0	0	0	0	590	0
7	64	M	+	+	+	7d	0	0	U	+	0	++	++	0	++(b)	0	0	—	0
8	65	M	0	+	+	10d	0	+	0	+	0	+	++	0	+	0	0	495	0
9	65	F	0	+	0	14d	+	0	0	+	0	+	+	+	0	0	0	—	+
10	69	F	+	0	0	28d	+	0	0	+	0	++(c)	+	+	0	0	0	435	0
11	71	M	+	+	+	21d	0	+	0	+	0	0	++	0	+	0	+(d)	560	+
12	76	F	+	0	0	14d	+	0	0	+	0	0	+	+	0	0	0	—	0
13	84	M	+	0	0	9d	+	0	0	+	0	+	++	+	0	0	0	510	0
14	58	M	+	+	0	—	0	0	C	0	+	++	++	0	++	+(FA)	0	—	+
15	61	M	+	0	+	19m	+	0	0	0	+	+	0	+	0	0	+	400	0
16	63	M	+	0	+	72m	+	0	0	0	+	++	+	+	+	0	0	450	+
17	63	M	+	0	0	—	0	0	CAD(h)	0	+	+	++	0	++	0	0	—	0(i)
18	66	F	+	0	+	2m	+	0	0	0	+	+	++	+	+	+	0	—	0
19	66	M	+	0	0	35m	0	0	MS	0	+	0	0	0	0	+	0	900	0
20	67	M	+	0	0	—	+	0	0	0	+	++	+	+	+	+	0	400	0
21	67	M	+	0	+	72m	+(f)	0	0	0	+	+	++	0	++	0	+	—	+
22	69	F	+	0	0	—	0	+	0	0	+	++	+	0	0	0	0	—	0
23	69	M	0	0	0	—	0	0	Cancer	0	+	+	+	0	0	0	0	330	0
24	76	F	+	0	0	—	0	+	0	0	+	+	+	0	++	+	0	610	0
25	78	M	0	0	0	—	0	0	CAD(g)	0	+	++	+	0	+	+	0	300	0
26	80	F	0	0	0	96m	0	+	0	0	+	++	+	0	++	+(CIA)	0	400	0
27	83	M	+	0	0	—	0	0	CAD	0	+	0	++	0	0	0	+	530	+
28	91	F	+	0	0	—	+	0	0	0	+	0	+	+	0	+	0	380	0
29	48	M	+	+(e)	0	—	+(e)	0	0	+e	+	+	0	0	0	0	0	440	0
30	52	M	+	+(e)	+	60m	+(e)	0	0	+e	+	+	+	0	++	+	0	500	0
31	63	M	+	+(e)	0	7m	+(e)	0	0	+e	+	0	++	0	+	0	+	550	+
Totals or Means	66	20M, 11F	25	13	9		18	5	8	16	18	22	28	14	15	9	5		7
(%)			81	42	29		58	16	26	52	58	71	90	45	48		16		23

A, acute; AAA, abdominal aortic aneurysm, fusiform, atherosclerotic origin; AD, aortic dissection; AR, aortic rupture; C, cirrhosis, alcoholic type; CIA, common iliac artery; d, days; F, female; FA, femoral artery; FC, false channel; H, healed; HW, heart weight; LV, left ventricular; M, male; m, months; MS, Marfan syndrome; RF, renal failure; TC, true channel; SH, systemic hypertension; u, uncertain; CAD, coronary artery dissection.

(a) One plus means the dissection involves only a portion of abdominal aorta; 2+ involves all the abdominal aorta.

(b) One plus indicates relatively small or mild, and 2+, relatively large or severe.

(c) Retrograde and antegrade aortic dissection.

(d) Earlier operative resection of the abdominal aortic aneurysm.

(e) Acute aortic dissection ruptured, not the healed one.

(f) Fusiform atherosclerotic abdominal aortic aneurysm ruptured, not the aortic dissection.

(g) Sudden coronary death outside the hospital.

(h) Acute myocardial infarction with fatal rupture of the left ventricular free wall.

(i) This was the only patient with an acute myocardial infarct.

TABLE 2. *Clinical and Morphologic Characteristics in Nine Patients Who Underwent Operative Therapy for Acute Aortic Dissection with the Entrance Tear in the Descending Thoracic Aorta*

Case	Age at Death (years)	Sex	SH (Hx)	Indication for Operation			Interval AD to Operation (days)	Operation		Interval First Operation to Death	Reop	Mode of Death			Entry Tear Upper 1/2	Involve Abdominal Aorta	Retrograde AD	Reentry Tear	HW (g)	LV Fibrosis
				H	Organ Ischemia	Other		Graft	Plication			H	I	Other						
1	66	M	+	+	0	0	6	+	0	0	0	+	0	0	+	+	0	0	495	0
2	39	F	+	0	+	0	1	0	+	<1 days	0	0	0	RF	+	+	0	0	460	0
3	69	F	+	0	+	0	4	0	0*	1 days	0	0	0	U	+	+	+	+	—	0
4	52	F	+	+	0	0	30	+	0	9 days	+	+	0	0	+	+	0	0	440	0
5	67	F	+	0	0	↑AD	9	+	0	9 days	0	+	0	0	+	+	0	0	295	+
6	65	F	+	–	–	–	≤30	+†	0	8 mos	+	+	+	0	+	0	0	0	455	+
7	46	M	+	0	0	AR	≤30	+	0	10 mos	0	0	+	0	+	+	+	+	470	0
8	71	M	+	–	–	–	≤30	+	0	14 mos	0	+	+	0	+	+	0	0	400	0
9	53	M	0	0	+	0	≤30	+	0	84 mos	0	+	0	0	–	+	0	0	429	+
Totals and means	66	4M 5F	8 89%	2	3	2	≤30	7	1	—	2	6	3	2	8	8	2	2	—	3

AD, aortic dissection; AR, aortic rupture; CHF, congestive heart failure; D, days; F, female; g, grams; H, hemorrhage; Hx, history; HW, heart weight; I, infection; LV, left ventricle; M, male; m, months; Op, operation; Reop, reoperation; RF, renal failure; SH, systemic hypertension; U, uncertain.

* Fenestration procedure creating a passage between the true and false aortic channels.

† The graft was placed in ascending aorta and aortic valve replacement was performed for aortic regurgitation due to retrograde dissection.

hospitals, 1 case each. No case came from the Clinical Center of the National Institutes of Health.

Results

Pertinent clinical and necropsy findings in each of the 40 patients are summarized in Table 1 (31 without operative therapy) and Table 2 (9 with operative therapy). The ages at death of all 40 patients ranged from 39 to 91 years (mean, 66 years); 24 were men and 16 were women. Systemic hypertension was apparent by history in 33 patients (83%) and the hearts were increased in weight in 78% (more than 350 g in women; more than 400 g in men).

Nonoperative Cases

Certain clinical and necropsy findings in these 31 patients are summarized in Table 1 and illustrated in Figures 1 to 13. Their ages ranged from 40 to 91 years (mean, 66 years); 11 were women and 20 were men. Systemic hypertension had been present by history in 25 patients (81%), and the hearts were of increased weight in 82%. Of the 29 patients, only 9 (29%) had the diagnosis of aortic dissection established during life. Of the 13 patients who had an aortogram performed, diagnosis of suspected aortic dissection was confirmed in 9 patients.

Acute Dissection

In 13 patients (42%) (numbers 1 to 13; Table 1, Figs. 1 to 4), the aortic dissection at necropsy was acute. The interval from onset of signs and symptoms compatible with acute dissection varied from 4 to 30 days (mean 12 days, median 9 days). In only 4 of the 13 patients was aortic dissection diagnosed clinically. Death resulted from rupture of the outer wall of the false channel in 9 of the 13 patients, from acute renal failure in 2 patients, and from uncertain causes in 2 patients.

At necropsy the entrance tear was in the proximal half of the descending thoracic aortas in all 13 patients, and in each of the nine who ruptured, the external rupture site was in the vicinity of the entrance tear. The rupture in each of the nine patients caused extravasation of blood into the left pleural space. The dissection extended into the abdominal aorta in eight patients, involving all of it in only two patients. The false channels contained thrombus in all 13 patients, relatively small amounts in 8 patients, and it filled all or most of the false channel in 5 patients. In 4 patients, all of whom had thrombi filling most or all of the false channels, the lumen of the true channel was severely compressed, producing what might be called true aortic stenosis. A re-entry tear was not identified in any of the 13 patients. In two patients (numbers 5 and 9, Table 1), the aortic dissection progressed retrogradely, as well as antegradely, and the adventitial hem-

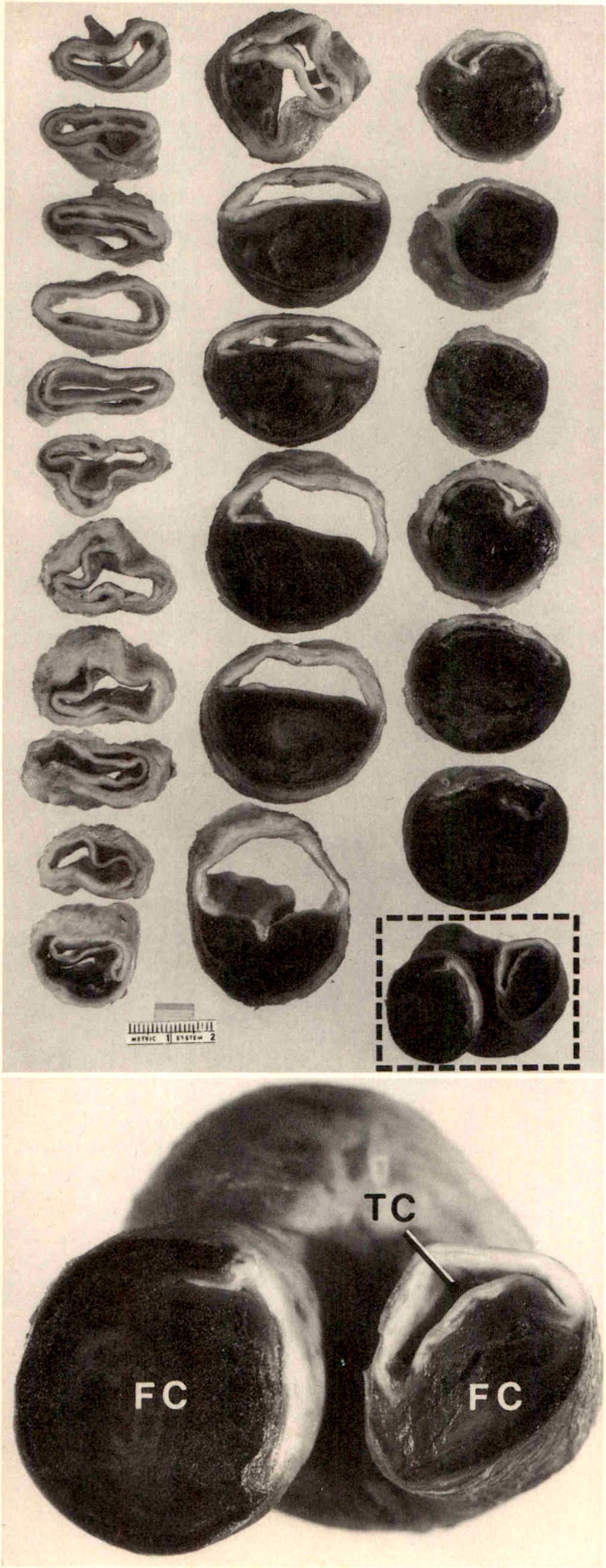

FIG. 1. (Case 7, Table 1). Serial cross-sections of aorta from the beginning of the descending thoracic aorta (top left) through the abdominal aortic bifurcation in a 64-year-old man (Howard #A79-40) who died of false channel rupture 7 days after onset of dissection with the entrance tear in the descending thoracic aorta. Thrombus occupies the entire false channel (FC) in the lower sections and compresses the true lumen, causing near-total obstruction of abdominal aorta. The close-up photograph (bottom) shows thrombus-filled false channels in each common iliac artery producing total true channel (TC) occlusion in one and partial true channel occlusion on the other.

orrhage was so extensive in one of these patients (number 9) that the mediastinum was widened, a finding that could have caused confusion with dissection from an entrance tear in the ascending aorta.[1-3] One patient (number 10) had an atherosclerotic fusiform aneurysm of the abdominal aorta that had been resected previously; the dissection, however, stopped 2 cm cephalad to the proximal graft suture line.

Healed Dissection

In 18 patients (58%), the dissection at necropsy had healed (numbers 14 to 31; Table 1, Figs. 5 to 13). The interval from onset of signs and symptoms compatible with acute dissection to death in the 7 patients in whom it was discernible ranged from 2 to 96 months (mean, 45 months; median, 35 months). Although 9 of the 18 patients had aortograms, in only 5 patients was aortic dissection diagnosed clinically. Death resulted from rupture of the healed false channel in 5 (28%) patients. Three additional patients (17%) (numbers 27, 28, and 29; Table 1) also died from rupture of the wall of the false channel, but the rupture site was the ascending aorta where a second acute new dissection had occurred. These three patients were the only ones who had both acute and healed aortic dissections. In each the entrance tear of the dissection that healed was the descending thoracic aorta, and the entrance tear for the fatal acute dissection was ascending aorta. Death in three patients (17%) resulted from chronic renal failure, which appeared to be the consequence of renal arterial compression by the large aneurysmal false channel. Of the remaining 7 patients, death was unrelated to the aortic dissection: 3 died from severe atherosclerotic coronary artery disease (1 suddenly, 1 from congestive heart failure, and 1 from left ventricular free wall rupture during acute myocardial infarction); 1 died from congestive heart failure, probably secondary to mitral regurgitation associated with the Marfan syndrome; 1 died of cancer; 1 of complications of alcoholic cirrhosis; and 1 of rupture of an atherosclerotic fusiform abdominal aortic aneurysm.

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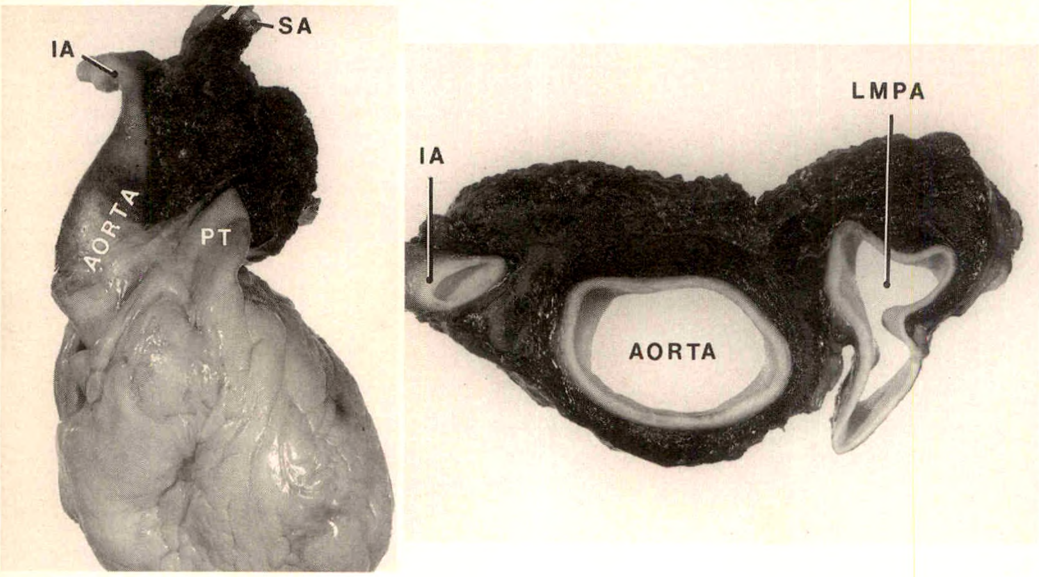


FIG. 2. (Case 10, Table 1) Photograph of heart and aorta of a 69-year-old woman (SH #A88-13) who had an entrance tear at the aortic isthmus with medial dissection to the common iliac arteries. In addition adventitial dissection occurred in a retrograde direction to ascending aorta and into the adventitia because both great arteries share a common adventitia. Left: Thrombus surrounds both aorta and pulmonary trunk (PT). SA = subclavian artery. Right: Cross-sections of aorta, left main pulmonary artery (LMPA), and innominate artery (IA) showing severe adventitial hemorrhage.

The entrance tear in 17 of the 18 patients was in the proximal half of the descending thoracic aorta. In the five patients with rupture of the wall of the 'healed' false channel, the rupture site was in the vicinity of the entrance tear. Of the patients with fatal rupture, the hemorrhage was into the left pleural space in four patients and into the esophagus in one (patient number 27) by a mechanism explained in Figure 11. The dissection involved the abdominal aorta in 14 patients with extension into 1 or both common iliac arteries in 6. The false channel contained thrombus in 15 of the 18 patients, and, in 6 of them, the thrombus occupied all or nearly all of the lumen of the false channel. Compression of the lumen of the true channel producing true aortic stenosis occurred in 10 patients. Re-entry tears were identified in 8 patients (44%) and were located in the aorta in 5, common iliac in 1, and common femoral artery in 1. Four patients had an atherosclerotic fusiform abdominal aortic aneurysm.

Operative Cases

Clinical and necropsy findings in the nine patients who underwent operation for aortic dissection are summarized

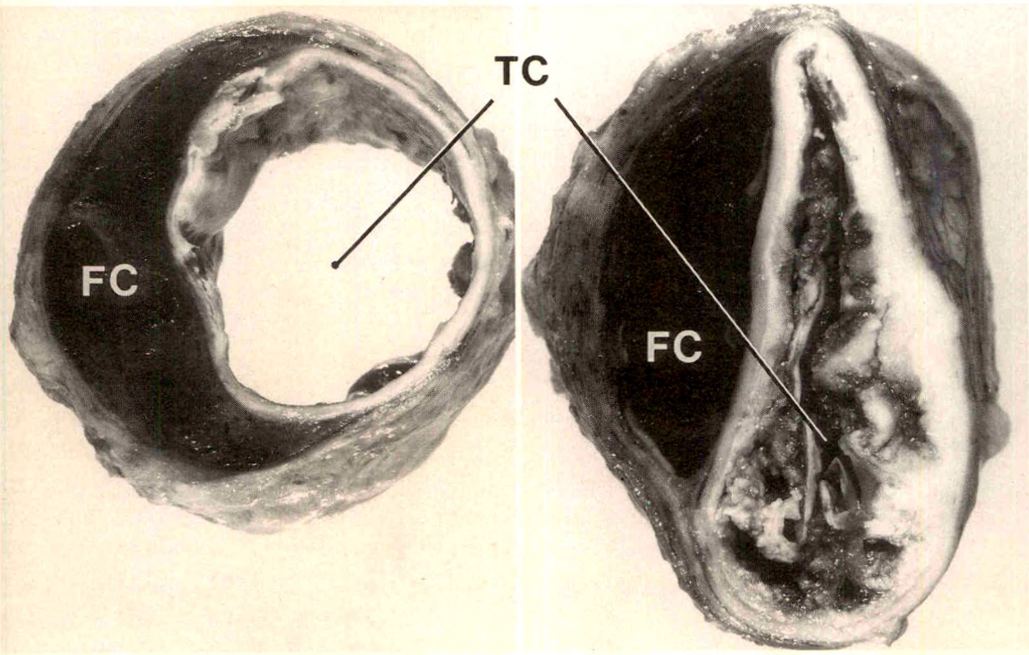
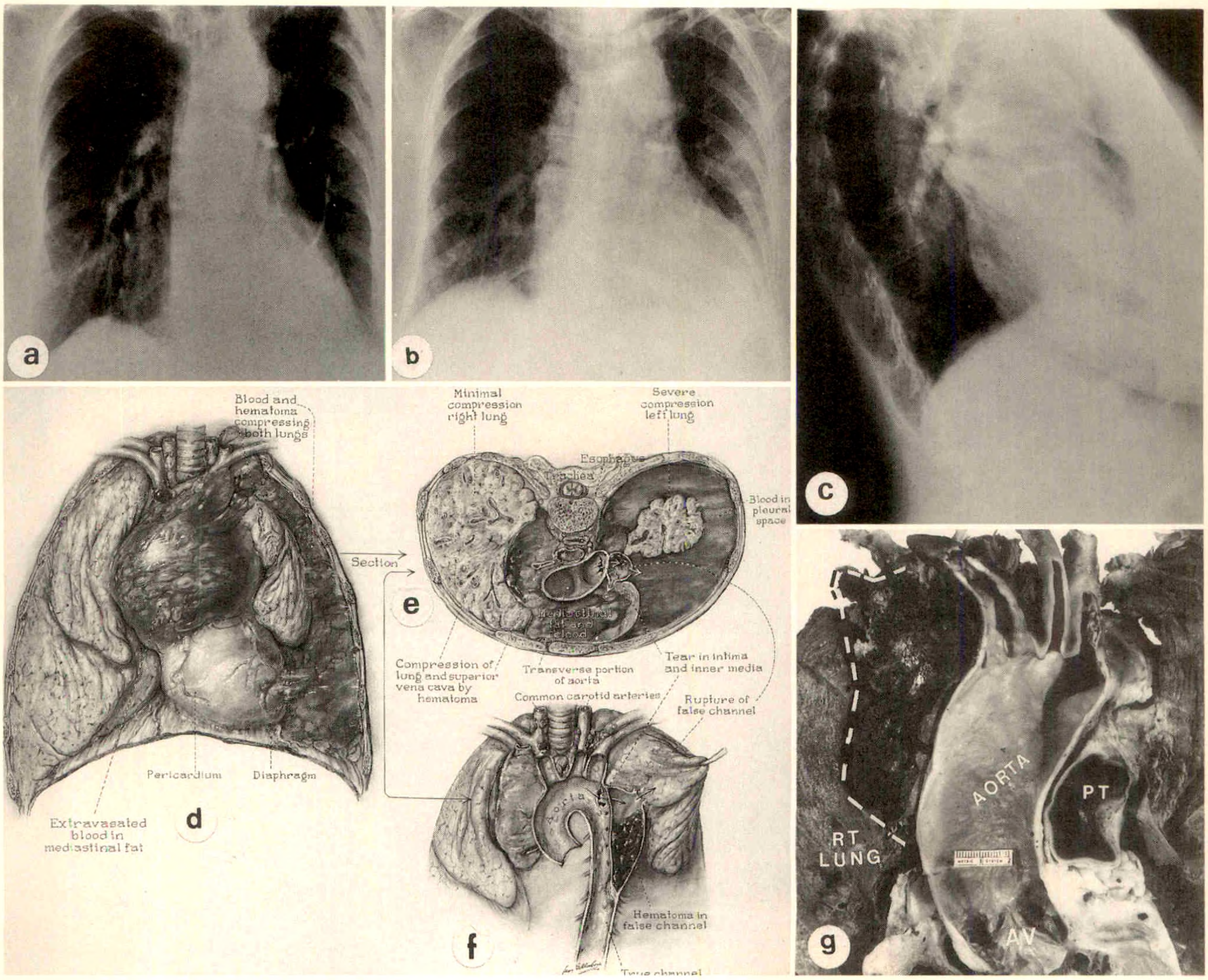


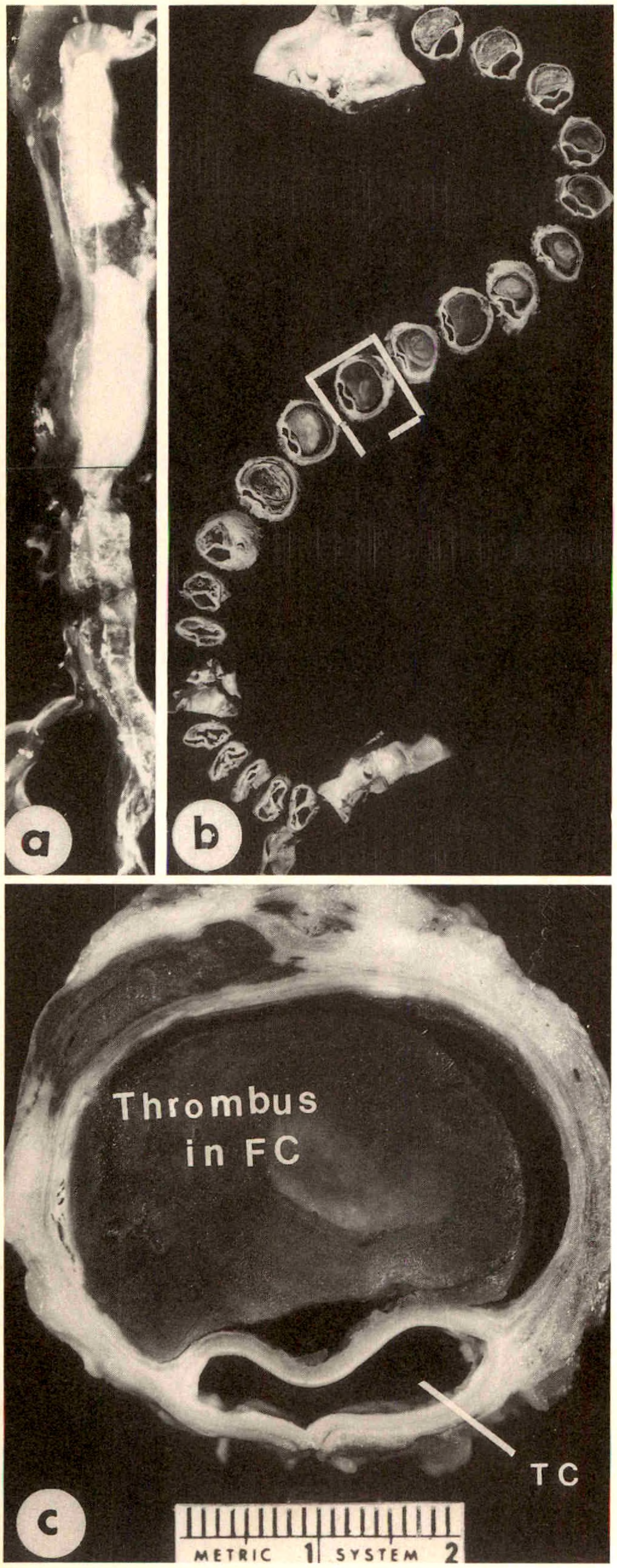
FIG. 3. (Case 11, Table 1). Photographs of two cross-sections of the descending thoracic aorta of a 71-year-old man (GT #82A-109) who died with renal failure 3 weeks after acute aortic dissection originating at the isthmus and extending to the level of the diaphragm. The false channel (FC) did not rupture. Death occurred from renal and cerebral dysfunction that resulted from pharmacologically induced hypotension. Left: The true channel (TC) is wide open but the false channel is filled with thrombus. Right: A more distal portion of aorta showing severe atherosclerosis of the true lumen and compression of its lumen by the thrombus in the false lumen.


a
b
c
Blood and hematoma compressing both lungs
Minimal compression right lung
Severe compression left lung
Esophagus
Trachea
Blood in pleural space
Section
e
Mediastinal fat and blood
Compression of lung and superior vena cava by hematoma
Transverse portion of aorta
Tear in intima and inner media
Common carotid arteries
Rupture of false channel
Pericardium
Diaphragm
Extravasated blood in mediastinal fat
d
Aorta
Hematoma in false channel
f
True channel
RT LUNG
AORTA
PT
AV
g

FIGS. 4a–g. (Case 12, Table 1). Acute dissection in a 76-year-old woman (GT #77A-173). The entrance site was the descending thoracic aorta with extravasation of blood into anterior mediastinal tissues simulating a dissection from a tear in the ascending aorta. The patient had been well until 14 days before death, when she noted epigastric pain and nausea. A chest radiograph (a) showed an abnormally shaped thoracic aorta. The electrocardiogram showed left ventricular hypertrophy, and her blood pressure was 200/100 mmHg. Because of previous esophageal stricture, her chest pain was believed to be related to the esophagus. She felt well thereafter until the day of death, when she suddenly noted dyspnea and profuse sweating; repeat chest radiographs (b and c) showed further widening of the mediastinum and markedly diminished lung space in the left hemithorax. Her heart stopped shortly thereafter. At necropsy the left lung was collapsed and most of the left hemithorax was filled with blood (d and e). A localized descending thoracic aortic dissection was present (f) and the entrance site into the false channel was at the aortic isthmus. The caudal two thirds of the false channel was filled with thrombus and the outer wall of the false channel was ruptured. Before the final extravasation of blood into the left hemithorax, blood appears to have dissected more slowly into the mediastinal tissues lying to the right of and anterior to the aorta. Hemorrhage into these mediastinal tissues on chest radiographs simulated dissection of the ascending aorta. (g) Close-up view of mediastinal hematoma to the right of the ascending aorta and behind the arch arteries. PT, pulmonary trunk; AV, aortic valve. (Reproduced with permission from Roberts WC. Aortic dissection: anatomy, consequences, and causes. Am Heart J 1981; 101:195–214.)

in Table 2. The ages of death ranged from 39 to 71 years (mean, 66 years); four were men and five were women. Of the 9 patients, 8 had had systemic hypertension by history and 7 had hearts of increased weight. The indication for operation in at least 7 of the 9 patients was a major complication of aortic dissection: 3 had limb or end-organ ischemia, 2 had hemorrhage into the left hemithorax, 1 had recurrent back pain with longitudinal progression of the dissection (by repeat aortogram), and 1 had aortic regurgitation from retrograde dissection. The interval from onset of symptoms or signs compatible with aortic dissection to operation was 30 days or less in all cases.

Three different procedures were performed in the 9 patients: tubular graft insertion in the descending thoracic aorta in 7 patients, obliteration of the false channel by suture in 1 patient, and a re-entry procedure in the distal portion of the dissected aorta in 1 patient.



FIGS. 5a–c. (Case 14, Table 1). Clinically silent healed dissection involving the descending thoracic and abdominal aorta in a 59-year-old man (NNMC #A76-87) who died from complications of habitual alcoholism. He was known to have had systemic hypertension. (a) Radiograph of aorta showing a narrowed true channel and thrombus plus heavy calcific deposits in the false channel. The entrance site was just distal to the aortic isthmus and the exit was in the left femoral artery. (b) Transverse sections of the aorta again showing that the true channel is narrowed by thrombus in the false channel. (c) Close-up view of the section in the brackets in b. TC, true channel; FC, false channel. (Reproduced with permission from Roberts WC. Aortic dissection: anatomy, consequences, and causes. Am Heart J 1981; 101:195–214.)

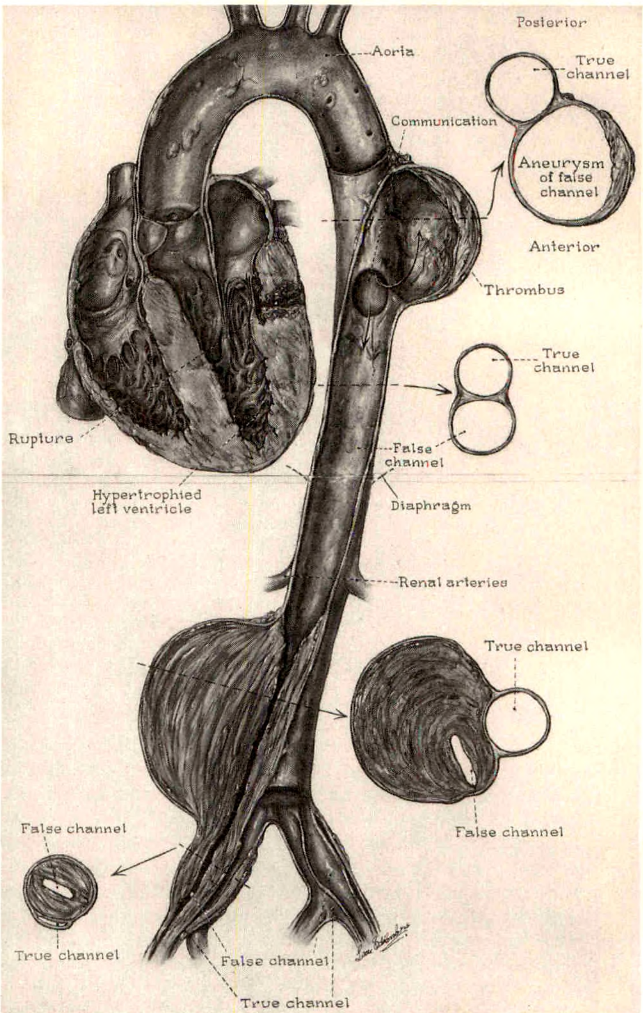
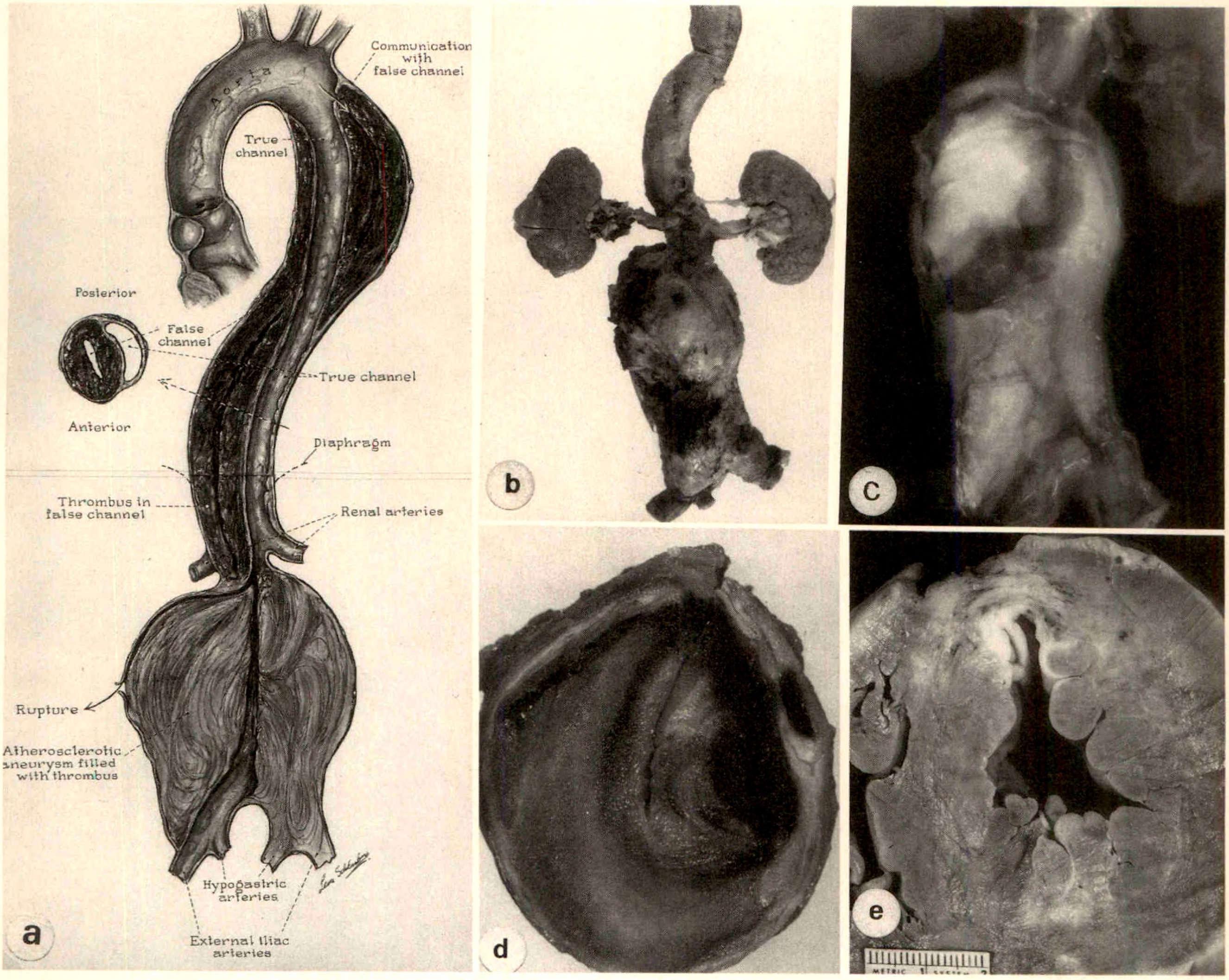


FIG. 6. (Case 17, Table 1). Asymptomatic healed dissection of the descending thoracic and abdominal aorta in a 63-year-old man (GW #8399) who died of rupture of the wall of left ventricle during acute myocardial infarction. There was no clinical evidence of an aortic dissection. He was known to have had systemic hypertension. He was asymptomatic until about 12 hours before death when he had the onset of chest pain of acute myocardial infarction. The drawing shows the entrance site into the false channel in the descending thoracic aorta and the false channel just caudal to this site developed a saccular aneurysm. The false channel in the abdominal aorta also became aneurysmal and filled with thrombus. The dissection extended into both common iliac arteries. The acute transmural myocardial infarct ruptured, causing massive extravasation of blood into the pericardial sac. (Reproduced with permission from Roberts WC. Aortic dissection: anatomy, consequences, and causes. Am Heart J 1981; 101:195–214.)

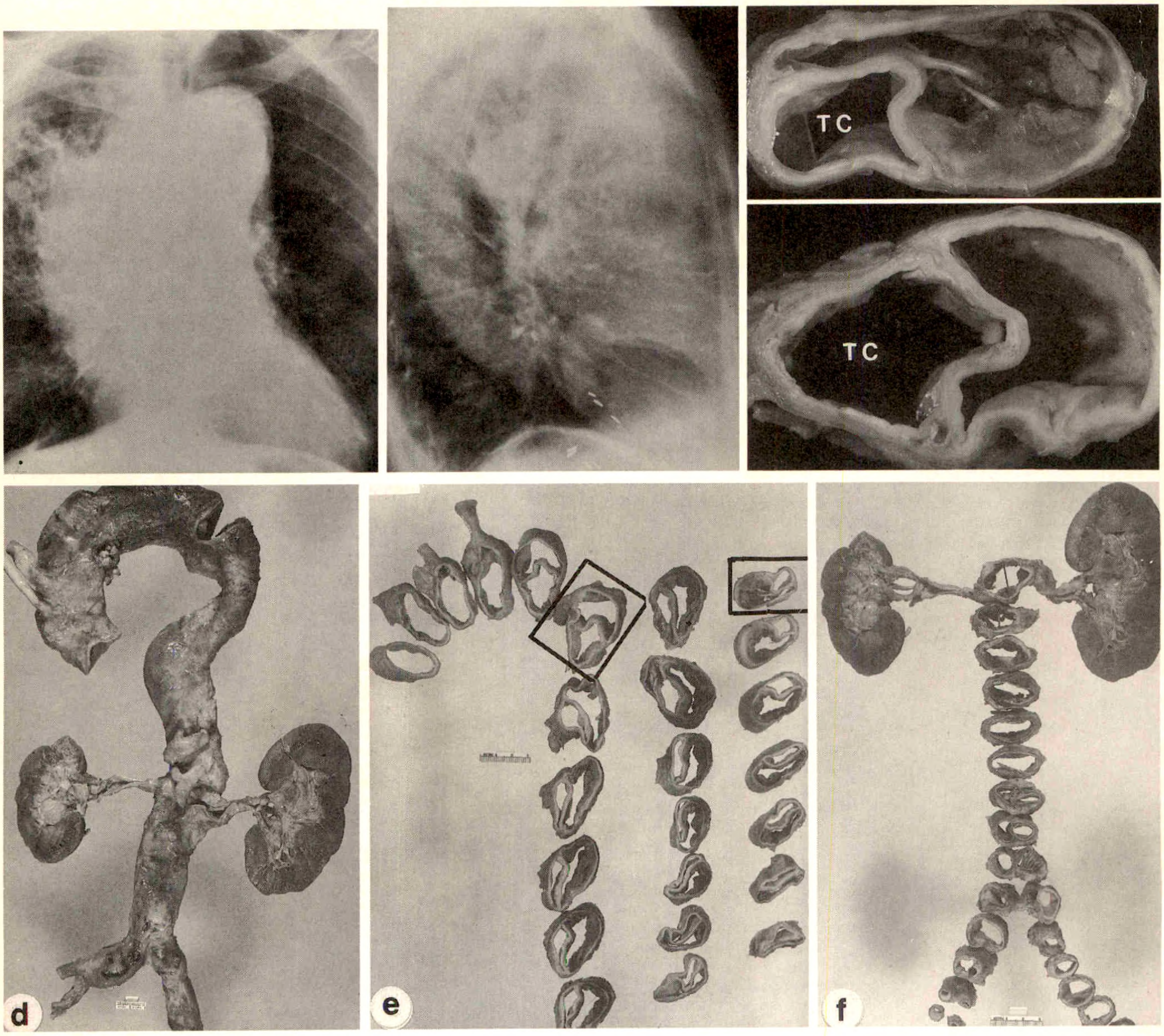


FIGS. 7a–e. (Case 21, Table 1). Rupture of a fusiform abdominal aortic aneurysm and healed dissecting aortic aneurysm together in a 67-year-old man (NNMC #A76-211). He had systemic hypertension for years and more than one acute myocardial infarct that had healed. Neither fusiform abdominal aortic aneurysm nor aortic dissection had been diagnosed clinically. (a) Drawing of the locations of the aortic aneurysms. The dissection stopped at the beginning of the fusiform abdominal aortic aneurysm and began just past the origin of the left subclavian artery. (b) Exterior view of the aorta, kidneys, and fusiform aneurysm. (c) Radiograph of fusiform abdominal aneurysm showing a few calcific deposits. (d) Transverse section of the abdominal aneurysm showing a severely narrowed lumen. (e) Transverse section of left ventricle showing a healed transmural infarct. (Reproduced with permission from Roberts WC. Aortic dissection: anatomy, consequences, and causes. Am Heart J 1981; 101:195–214.)

Five of the nine patients died within 9 days of operation: the mode of death was hemorrhage in 3, acute renal failure with anuria (both before and after operation) in 1, and unclear in 1. All 5 patients who died early had major preoperative complications of dissection that probably would have resulted in death: hemorrhage in 2 patients, organ ischemia in 2, and progression of dissection in 1. Four of the nine patients died late (at 8 to 84 months). The mode of death was aortic hemorrhage in three patients; infection in two of them led to anastomotic breakdown; and in the third patient, an unreplaced portion of false channel ruptured. The only patient in whom the aorta or aortic anastomosis did not rupture died of infection.

Discussion

Analysis of the aforementioned 40 necropsy patients with aortic dissection resulting from an entrance tear in the descending thoracic aorta disclosed that 13 of the patients died within 30 days of the event without operative intervention, 9 others underwent operative therapy during the acute phase because of complications of the dissection, and in 18 patients the dissection healed without operative



FIGS. 8a–f. (Case 23, Table 1). Clinically silent aortic dissection after resection of an abdominal aortic fusiform aneurysm in a 69-year-old man (DCVAH #78A-178) who died of bronchogenic carcinoma. The abdominal aorta was replaced with a graft about 1 year before death. Dissection of the aorta stopped at the beginning of the graft. There was no history of systemic hypertension, and the heart weighed only 330 g. Chest radiographs (a and b) shortly before death; aorta, common iliac arteries, and kidneys (d); cross-sections of aorta to the renal arteries (e) and below (f), which include the Dacron graft. The dissection began at the aortic isthmus. The false channel is larger than the true channel. Thrombus is present in some portions of the false channel (c). Close-up views of the two-bracketed cross-sections are shown in e. (Reproduced with permission from Roberts WC. Aortic dissection: anatomy, consequences, and causes. Am Heart J 1981; 101:195–214.)

intervention. The nine patients who underwent operative therapy during the acute phase probably would have died from the acute complication that led to the operation. Thus, of the 40 patients, less than one half (45%) survived the acute period to 'heal' the dissection.

Compared to dissections resulting from tears in the ascending or transverse aorta, dissection with the entrance tear in the descending thoracic aorta has the highest frequency of healing. Among our 182 necropsy patients with aortic dissection, the entrance tear was the ascending aorta in 128 patients and only 8 (6%) healed; the entrance tear was the transverse aorta in 12 patients and none healed. Other comparative information virtually is impossible to acquire from previous publications because the site of the entrance tear was not the basis for classifying the type of dissection, and the site of the entrance tear was not always

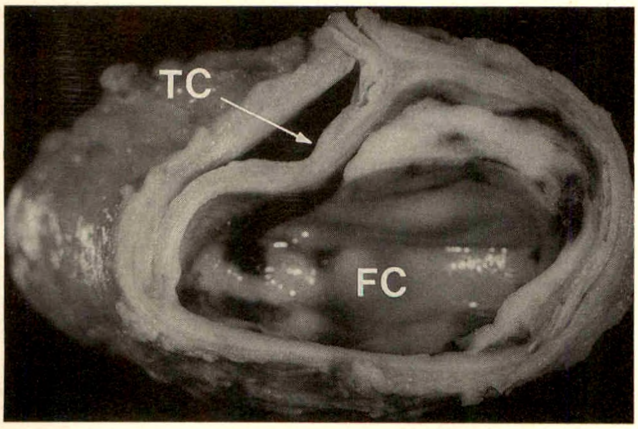
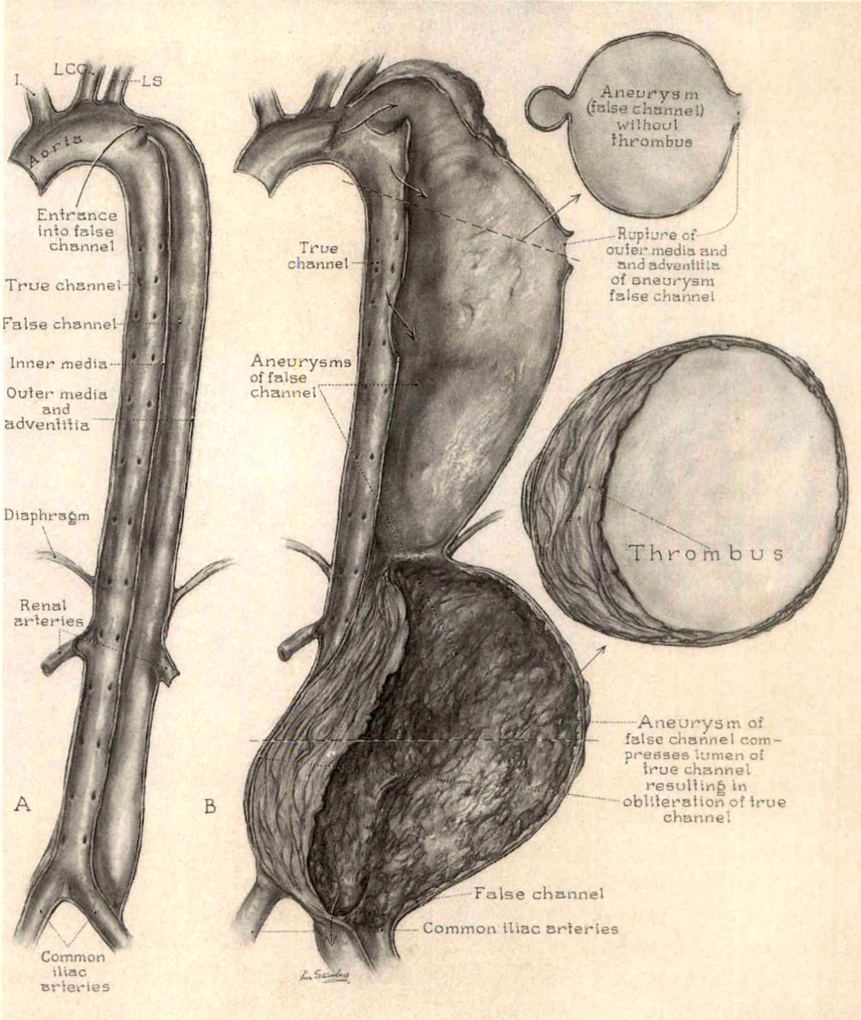


FIG. 9. (Case 24, Table 1). Cross-section of dissected descending thoracic aorta in a 76-year-old woman (GT #76A-147) who died of renal failure. The true channel is stenotic from compression from thrombus in the false channel. FC, false channel; TC, true channel.

clarified. In Shennan's 1935 monograph,[4] for example, of 309 necropsy cases of aortic dissection reviewed (only 28 of which actually were studied by the author), 233 (75%) patients died acutely, and in 79 (25%) patients the dissection healed. Of the latter 79 patients, the dissection did not involve the ascending aorta in 46 (58%), but tears involving either the arch or descending thoracic aorta were not separated. Furthermore the percentage in whom the dissection was retrograde was not delineated. Nevertheless this older report and others[5–7] indicate that dissection resulting from tears in the ascending aorta infrequently heal and that those originating from tears in the descending thoracic aorta heal more frequently.

Late complications, *i.e.*, those after 'healing' of aortic dissection, are far more common with dissection caused by an entrance tear in the descending thoracic aorta then in those caused by an entrance tear in the ascending aorta


I.
LCC
LS
Aorta
Entrance into false channel
True channel
False channel
Inner media
Outer media and adventitia
Diaphragm
Renal arteries
A
Common iliac arteries
True channel
Aneurysms of false channel
B
Aneurysm (false channel) without thrombus
Rupture of outer media and and adventitia of aneurysm false channel
Thrombus
Aneurysm of false channel compresses lumen of true channel resulting in obliteration of true channel
False channel
Common iliac arteries

FIGS. 10A and B. (Case 26, Table 1). Drawing of healed dissection with entrance tear at the isthmus in an 80-year-old woman (GW #7754). (A) Early after healing. (B). At time of necropsy. The false channel reached enormous size and compressed the true channel. The abdominal aortic aneurysm was of the false channel, although it might be confused easily with an atherosclerotic fusiform abdominal aortic aneurysm. A re-entry tear was located in the left common ilian arter. I, innominate artery; LCC, left common carotid; LS, left subclavian.

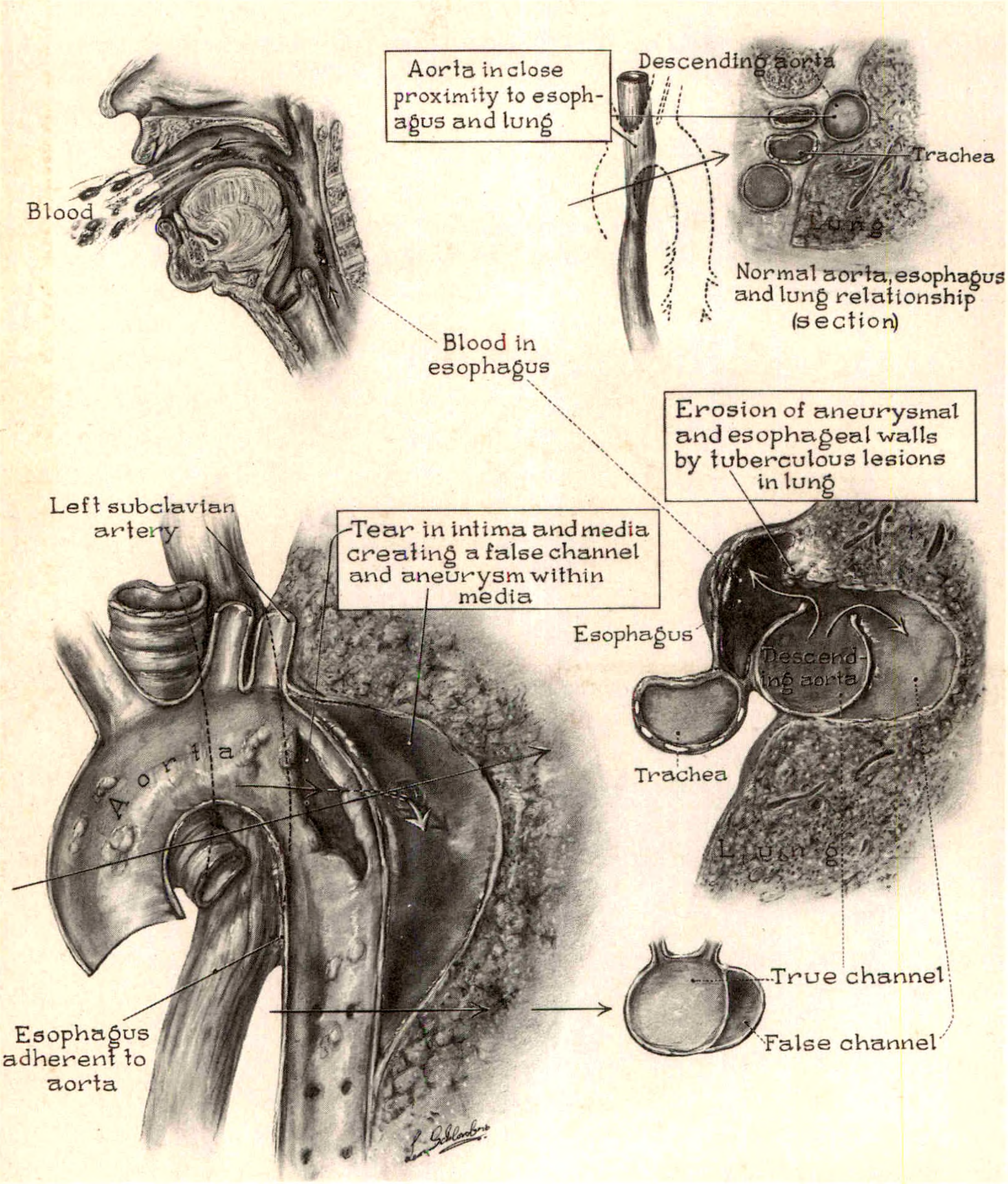

Aorta in close proximity to esophagus and lung
Descending aorta
Trachea
Lung
Blood
Normal aorta, esophagus and lung relationship (section)
Blood in esophagus
Erosion of aneurysmal and esophageal walls by tuberculous lesions in lung
Left subclavian artery
Tear in intima and media creating a false channel and aneurysm within media
Esophagus
Descending aorta
Trachea
Aorta
Lung
True channel
False channel
Esophagus adherent to aorta

FIG. 11. (Case 28, Table 1). Drawing of a dissected descending thoracic aorta with entrance tear in descending thoracic aorta in a 91-year-old woman (GT #80A-126). She collapsed and was found with blood ejecting from her mouth. Necropsy disclosed that the lungs were infected by tuberculous bacilli and that the left lung was adherent to the descending thoracic aorta. The pulmonary infection was the medium that allowed the aorta to rupture into the esophagus, to which it was adherent. (Reproduced with permission from Roberts WC. Aortic dissection; anatomy, consequences, and causes. Am Heart J 1981; 101:195–214.)

or transverse aorta. Although aortic dissection with ascending aortic entrance tear is just more than three times as common as that resulting from descending thoracic aortic entrance tear, the frequency of healing in the former group is just less than 10% and that in the latter group, nearly 50%. Thus to produce 20 cases with healing of the dissection from an entrance tear in the ascending aorta would require 250 cases of that type; in contrast to produce 20 cases with healing of the dissection from an entrance tear in the descending thoracic aorta would require about 40 cases of that type. Because most patients with diagnosed dissection from an entrance tear in the ascending aorta now undergo immediate operative therapy, data on healing is difficult to obtain. In contrast, because most patients with diagnosed dissection from an entrance tear in the descending aorta do not undergo operative therapy, data on healing in this group is easier to acquire. Consequently complications after healing of the aortic dissection, for practical purposes, are limited to the group in which the entrance tear is the descending thoracic aorta.

Of the various late complications after healing of aortic dissection with a descending thoracic entrance tear, the most common is aneurysmal formation of the false channel, which occurred in all 18 of our patients with healed dissection. The larger the aneurysm of the false channel, the greater the likelihood of rupture of the wall of the false

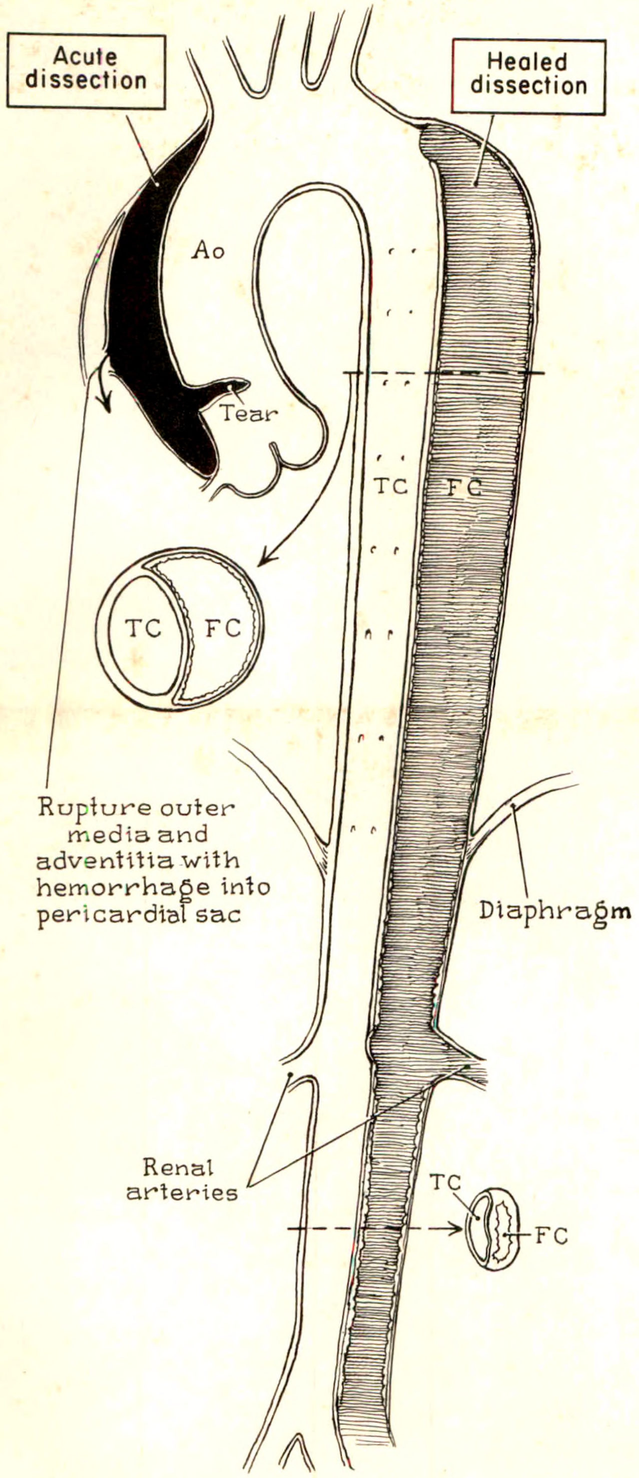


FIG. 12. (Case 29, Table 1). Drawing of aorta in a 48-year-old man (NCBH #A15-837) who died of rupture of the wall of the false channel after acute dissection with an entrance tear in ascending aorta. Found incidentally at necropsy was a healed dissection of the entire descending aorta with an entry tear at the isthmus. The patient's son died at 28 years of age, also from acute aortic dissection. (Reproduced with permission from Warnes CA, Kirkman PM, Roberts WC. Aortic dissection in more than one family member. Am J Cardiol 1985; 55:236–238.)

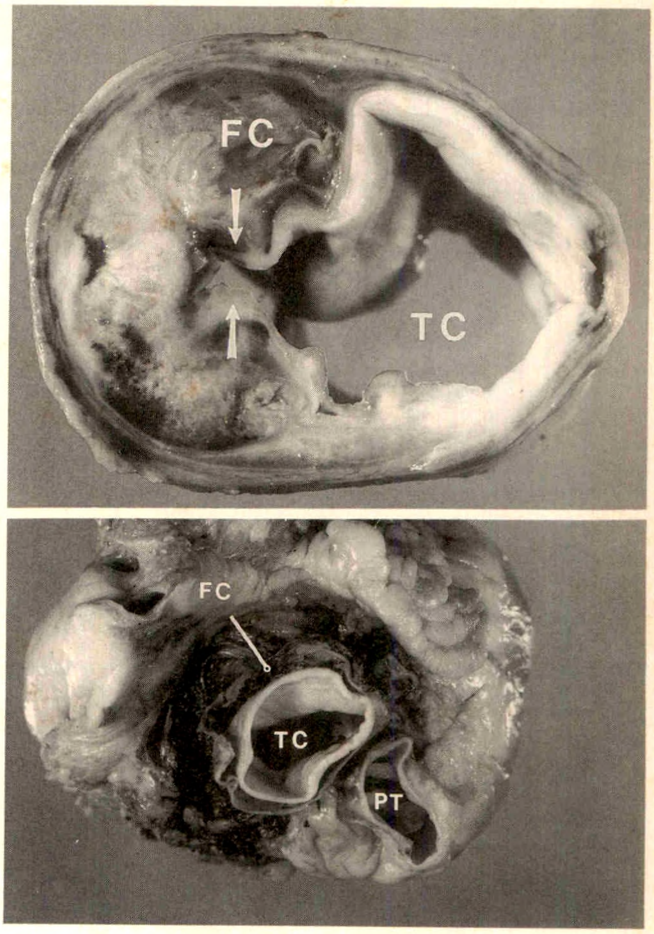


FIG. 13. (Case 31, Table 1). Photograph of aorta (upper) and heart (lower) of a 63-year-old man (SH #A86-34) with systemic hypertension who died of ruptured acute dissection with entrance tear in the ascending aorta. At necropsy, a healed dissection with an entry tear at the isthmus also was present. Upper: Cross-section of the dissected, healed descending thoracic aorta. The false lumen (FC) is filled with organized thrombus and it does not significantly compromise the true lumen (TC). The arrows designate the entrance tear. Lower: View of heart from above showing the acute dissection with false channel filled with recent thrombus.

channel, which occurred in five patients. The fact that the wall of the false channel may rupture late has received little attention previously. The presence of a re-entry tear did not appear to protect the healed dissection group from rupture of the false channel. Of the 18 patients with healed dissection, 9 had a re-entry tear: 3 ruptured the wall of the false channel exteriorly and 6 did not. Because thrombus was so frequently present (15 patients) in the false channel in the 18 patients with healed dissection, no relation was found between its presence and aneurysmal formation of the false channel or an exit tear in the partition between the true and false channels. Renal failure (3 patients) appeared to be the consequence of compression on one or both renal arteries by the aneurysmally dilated false channel. Obstruction of the lumen of the true channel occurred in 11 of the 18 patients with healed dissection. All 11 patients with true channel stenosis had thrombi in the false channel, and none of the three patients without false channel thrombus had true channel stenosis. The narrowing of the true channel appears to be the consequence of compression from the thrombus-containing false channel. Hemodynamic confirmation of true channel stenosis in this circumstance is not available. The wall of the false channel calcified in 1 of the 18 patients. Because the acute dissection in this patient was clinically silent, the interval from the acute dissection to death is unknown. And finally an acute dissection with an entrance tear in the ascending aorta occurred in 3 of the 18 patients with a healed dissection from a descending thoracic aortic entrance tear. That healed aortic dissection may later, for reasons unclear, predispose to another acute dissection elsewhere in the aorta also has received little attention previously.

The aorta with dissection, of course, is not immune to other diseases of the aorta. Of our 40 patients, 5 had a fusiform atherosclerotic aneurysm of the abdominal aorta, and in all of them the dissection terminated at or proximal to the atherosclerotic aneurysm. One of the forty patients had typical clinical features of the Marfan syndrome. Although the ascending aorta was dilated in this patient, the entrance tear was in the descending thoracic aorta only, and the dissection involved only the descending thoracic aorta. In contrast to their occasional occurrence in patients with dissection from an entrance tear in the ascending aorta, none of the 40 patients with an entrance tear in the descending thoracic aorta had a bicuspid aortic valve or aortic isthmic coarctation.

Throughout this article we focused on the location of the entrance tear and not on the portion of the aorta involved by the dissection. We believe this focus is appropriate because the site of the entrance tear is the major determinant of the frequency of healing of the dissection, the mode of death, and the operative approach.

The relatively high frequency of healing of aortic dissection with a descending thoracic aortic entrance tear and the relatively high operative mortality rate in this group caused Wheat and associates[8] in 1965 to advocate nonoperative intervention for this type of dissection.[9,10] This viewpoint, with some exceptions,[11–15] has dominated therapy for aortic dissection of this type since that time.[16–21] Operative mortality rates have remained relatively high (compared to those for dissection originating from a tear in the ascending aorta), but usually operation was not carried out for this type of dissection unless a recognized complication occurred. Thus the mortality rate for early operative intervention for dissection with a descending thoracic aortic entrance tear without complications may be considerably lower than that when operation is not performed until one or more complications develop.[12] Nevertheless, without operative therapy, more than 50% of the patients with this type of dissection die during the acute phase and most of those who heal develop complications that in themselves later warrant operative intervention. Thus we believe that, in balance, early operative therapy will allow a much greater survival rate than will nonoperative therapy.

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BOOK REVIEWS

William P. Longmire, Jr., M.D.
Advisor for Editorial Board
Los Angeles, California

H. Kim Lyerly, M.D.
Advisor for Residents in Surgery
Durham, North Carolina

The Story of Thoracic Surgery: Milestones and Pioneers. Andreas P. Naef. 160 pp. Toronto: Hogrefe and Huber, 1990. $19.80.

ANY MEDICAL STUDENT, internist, surgeon, or layman with the slightest interest in medical history or the development of cardiothoracic surgery will find this small volume a delightfully written treasure of facts and events, and of Professor Naef's personal encounters with many of those pioneers who have brought this discipline to its present advanced stage. As the author states, 'There are two ways to approach the history of cardiovascular surgery. One option would be a step-by-step review of the progressively sophisticated techniques developed during the last 50 years in conjunction with modern science and technology.' Instead Professor Naef elected a different goal, 'namely, to follow the leading figures [most of whom he knew personally] on their fascinating journey to modern heart surgery [and other fields of thoracic surgery] as they pass the major milestones showing the way toward progress.'

There will, undoubtedly, be a few contributors, although certainly not many, who feel slighted in this historical account. But Professor Naef compiled an amazing array of facts and supporting documentation in an effort to record the significant events, and to assign appropriate priority to contributors, in this story of the still-evolving field of thoracic surgery.

Professor Naef's interesting literary style is supported amply by the publisher's clear type and many photographs and drawings, most of which are well reproduced.

The book will provide the reader not only with a fascinating true story but it will also serve as a continuing source for many important historical references.

WILLIAM P. LONGMIRE, JR., M.D.
Los Angeles, California

Lasers in Gastroenterology: International Experiences and Trends. J. F. Riemann and C. Ell. 164 pp. Sutuugart: Georg Thieme Verlag, 1989. $65.00.

I WAS VERY PLEASED to review *Lasers in Gastroenterology: International Experience and Trends* edited by Riemann and Ell. This is an excellent review of the field of laser applications in gastrointestinal diseases. The editors compiled chapters from world authorities in the field to contribute several outstanding chapters.

Chapter 1 is an excellent review covering some of the basic physics principles of laser technology. It specifically concentrates on the applications to gastroenterology and also some of the pathologic changes in tissues caused by laser energy.

The chapter on the upper gastrointestinal tract is outstanding. The only criticism I have regards a reference on page 28 to use of ice-cold saline lavage, which certainly is outdated when dealing with upper gastrointestinal bleeding. In addition the authors show more enthusiastic about laser hemostasis for upper GI bleeding than exists in the rest of the world literature.

Although the chapter on the biliary tract is well written, aside from laser lithotripsy of common duct stones, the other applications do not appear to offer an advantage over electrocautery.

The chapter on the lower GI tract represents a large clinical experience on the endoscopic management of difficult tumors. The data presented is certainly outstanding and rivals any other nonoperative management of these tumors.

There are three small chapters on photodynamic therapy. This therapy has many future applications but is in its infancy stages. The chapters on combined therapy with laser and future trends both are well written and represent complete reviews of the literature.

This textbook is short, a total of 164 pages, but represents a complete review of the endoscopic applications of laser technology in the gastrointestinal tract. It can certainly serve as an up-to-date resource for the reader looking for the newest innovations in laser endoscopic therapy.

THEODORE N. PAPPAS, M.D.
Durham, North Carolina

Reflux Oesophagitis. T. P. J. Hennessy, A. Cuschieri, and J. R. Bennett. 199 pp. Stoneham, MA: Butterworths, 1989. $110.00.

THIS SMALL BOOK, despite its title, deals with much more than reflux esophagitis. It aims to give a 'balanced and concise account of current thinking on the nature and problems of gastro-oesophageal reflux disease.' The editors, two surgeons and a gastroenterologist, are well-known contributors in the field.

There are substantial chapters on the pathophysiology of gastroesophageal reflux disease, investigation, and surgical treatment. Clinical features, motility disorders associated with reflux, medical treatment, and the treatment of complications receive briefer but still detailed consideration, and there is a separate chapter on Barrett's esophagus. Some overlap between chapters is inevitable if each is to stand as a coherent section in its own right, and this is not usually obtrusive except in the short chapter on clinical features that includes details of laboratory testing, a topic dealt with extensively later in the text.

The content of each chapter is current and the views expressed are mostly well balanced. All chapters are well referenced, averaging about 130 references (range, 62 to 237 entries) per chapter. These comprehensive bibliographies contain many recent references as well as key citations from the past 30 years. While it would seem churlish to complain at such abundance, this approach inevitably entails a superficial treatment of disputed matters. For example the authors seem disposed to accept uncritically the results of studies obtained using the Dent sleeve and imply that the discovery of Transient Lower Esophageal Sphincter Relaxations has settled the controversy as to how reflux can occur in the face of a normal basal sphincter pressure. The significance of other features of the LES such as total length and abdominal length perhaps is not adequately appreciated. Some readers may be surprised to see Professor Cuschieri's unsupported assertion that Nissen fundoplication has a failure rate of 40%. Most surgeons would regard the claim as extravagant. However he is right to draw attention to the complications of the procedure other than recurrent reflux. His personal recommendation for an incomplete fundoplication for uncomplicated reflux is not supported by any long-term studies comparable to those for the Nissen procedure and is in conflict with the known lack of durability of partial fundoplication procedures. Other caveats are minor. There are some typographic errors in the text and references that lead to occasional ungrammatical constructions but not to loss of meaning or clarity.

These considerations notwithstanding, the editors produced a clear, contemporary, and comprehensive account of gastroesophageal reflux disease and its investigation and treatment that will make useful and enjoyable reading for all surgeons who treat this condition.

TOM R. DEMEESTER, M.D.
PETER F. CROOKES, F.R.C.S.
Los Angeles, California

Surgery of the Chest, 5th Edition (2 volumes). David C. Sabiston, Jr. and Frank C. Spencer. 2084 pp. Philadelphia: WB Saunders, 1990. $250.00.

Gibbon's textbook, now published in its 5th edition, covers the results of almost 30 years of exciting developments in the art and science of chest surgery. Again superbly edited by D. C. Sabiston, Jr. and F. C. Spencer, it now contains 58 chapters in two volumes comprising almost 2000 pages, for which a total of 114 authors sign responsible. Some of the more important subjects, such as coronary artery disease, are subdivided in sections and subsections. The individual chapters and their fractions are written by almost exclusively North American authors of world rank. The need for continuous updating of the material is well met by the addition of four new chapters (P. K. Smith: "Computer Application in Cardiac Surgery"; H. K. Lyerly and J. A. Bartlett: "Thoracic Disorders in the Immunocompromised Host"; R. J. Herfkens: "Role of Magnetic Resonance Imaging in Cardiovascular Diagnosis"; and F. L. Dunn and P. B. Morris: "Dietary and Pharmacologic Management of Atherosclerosis"), as well as the acquisition of 30 new authors. The material presented may be subdivided roughly into topics of general importance (459 pages or 23%), thoracic surgery (611 pages or 31%), and cardiac surgery (909 pages or 46%), which overlap to the extent that neither of the two volumes stands alone.

The scope of the general topics of the textbook but also of most of the individual chapters goes far beyond the actual art of surgery but includes the impact of clinical and basic science in this field. Nevertheless there is an adequate balance between the basic knowledge a modern surgeon is expected to possess when conducting his or her operative procedure (pathology, pathophysiology, diagnostics, indications, and perioperative management) and results. In that sense the textbook offers an invaluable reference source of encyclopedic format. The operative techniques generally are well described and illustrated in their principles, but the textbook does not and can not equal an atlas of operative techniques, their variances, and pitfalls. Each chapter contains a bibliography of the most important contributions to the individual subject, thereby facilitating in-depth reading.

For someone like myself, a non-American cardiothoracic surgeon, who has learned much from Gibbon's surgical text, it is a pleasure to recommend this newest edition of Gibbon's textbook to upcoming and to established cardiothoracic surgeons as well as to their partners in the neighboring fields.

Professor HANS G. BORST
Hannover, Federal Republic of Germany

LETTERS TO THE EDITOR

June 24, 1990

Dear Editor:

Drs. Lohmuller, Pemberton, Dozois, Ilstrup, and Van Heerdon in their article "Pouchitis and Extraintestinal Manifestations of Inflammatory Bowel Disease After Ileal Pouch-Anal Anastomosis" discuss the relationship between pouchitis, extraintestinal manifestations, indeterminate colitis, and Crohn's disease.[1] They do not mention the autoimmune response mechanism and immunosupressive therapy that may be a common factor. Present[2] assumes a 5% to 10% failure with the present surgery and suggests a medical trial before extensive surgery. His indications for the use of immunosurpressive therapy include (1) failure to respond to steroids and sulfasalazine; (2) steroid toxicity and continuous steroids for Crohn's disease; (3) patients with proctosigmoiditis who have not responded to oral and topical therapy; and (4) patients with left-sided or universal disease who are continually active and have not had disease long enough to be at risk for carcinoma of the colon. He has found 6-MP and azathioprine to be effective in 60% to 70% of patients and toxicity infrequent and reversible and no definite increase in superinfections or neoplasms in long-term use.

Cyclosporin is under investigation and does seem to show promise for inflammatory bowel disease (IBD) as it does for organ transplant immunosupressive therapy.[3] According to Riskin et al.,[4] synthetic carbohydrates may represent an important new class of drugs for the treatment of inflamatory, autoimmune diseases. Effectiveness of these drugs should lend credence to the theory that the nature of IBD is autoimmune and add another dimension, besides surgery, to its treatment.

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LAWRENCE BRASLOW, M.D.
Riverside, California

August 28, 1990

Dear Editor:

In response to Dr. Lawrence Braslow's comments regarding our article, we would point out that the purpose of our study was not to investigate the etiology of ulcerative colitis nor its medical management but rather to study the relationship we have seen between pouchitis and extraintestinal manifestations of ulcerative colitis after ileal pouch–anal anastomosis. Be that as it may, at the conclusion of our discussion we do, in fact, suggest that the pathophysiologic mechanisms involved in pouchitis may be similar to those involved in chronic ulcerative colitis. Of course it is highly speculative whether this is an autoimmune process or some other mechanism.

Although Dr. Braslow's comments are appreciated, we cannot speak to them because they involve a subject far broader than our study.

JOHN H. PEMBERTON, M.D.
JOSEPH L. LOHMULLER, M.D.
Rochester, Minnesota

September 10, 1990

Dear Editor:

I read with interest the paper by Dr. Klein and colleagues entitled "Current Management of the Budd-Chiari Syndrome" in the August 1990 issue of *Annals of Surgery*.

In their discussion they did not mention the nonsurgical treatment of Budd-Chiari syndrome. The authors listed several causes of hepatic venous outflow occlusion, including membranous obstruction of the suprahepatic inferior vena cava. The latter, which is more common in the Orient, is suited ideally for nonoperative treatment by percutaneous balloon dilation. My colleagues from China and I have now successfully treated six such patients, three of whom had previous surgical procedures. Improvement was dramatic and long lasting.

Therefore, in the current management of the Budd-Chiari syndrome, one form, specifically membranous obstruction of inferior vena cava, which can be accurately diagnosed by angiography, could and should be treated nonsurgically by percutaneous balloon dilation. The latter approach is an effective and safe alternative to surgery.

TSUNG O. CHENG, M.D.
Washington, D.C.

October 2, 1990

Dear Editor:

Obstruction of hepatic venous drainage can result from disease at several anatomic locations including (1) nonthrombotic veno-occlusive disease originating in the terminal hepatic venules, (2) thrombotic occlusion of the hepatic veins or suprahepatic vena cava, and (3) membranous obstruction of the suprahepatic inferior vena cava. It has been common practice to group this diverse array of disorders together as the Budd-Chiari syndrome. Much of the confusion and debate concerning the optimal treatment for these patients could be avoided if such practice was abandoned.

I would agree with Dr. Cheng that invasive radiologic techniques may be appropriate treatment for selected patients who develop isolated membranous obstruction of the suprahepatic vena cava, and the successful outcome of such strategy has been published previously.[1,2] Percutaneous laser-assisted angioplasty has also been used in similar cases.[3,4] Membranous vena caval obstruction, although a common etiology of the Budd-Chiari syndrome worldwide, is rare in the United States except in those areas with a large population of Oriental immigrants.[5] Our discussion concerning the surgical management of patients with the Budd-Chiari syndrome was directed toward patients with hepatic vein thrombosis that was either primary in nature or developed secondary to vena caval obstruction. Neither balloon angioplasty nor laser obliteration is likely to be safe or effective for such patients, who account for the majority of Budd-Chiari cases seen in this country. There may be, however, a role for invasive radiologic procedures in the postoperative management of these patients. In our experience both anastomotic and non-anastomotic venous stenoses have been managed successfully with a combination of percutaneous transluminal angioplasty and/or percutaneous transvenous stent placement.

ANDREW S. KLEIN
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August 9, 1990

Dear Editor:

It seems to me that Drs. Crowley and Seigler, the authors of "Late Recurrence of Malignant Melanoma" (August 1990), missed an excellent opportunity to make a contribution to the debate concerning the current concept of local excision of thin melanomas of that amount of tissue that can be closed primarily is sufficient in a 10-year follow-up study. They indicated in their article, as I read it, that tumors less than 1 mm in depth represented approximately 25% of their cases (this was illustrated in Table 2.) In Table 4 they indicated that local skin recurrence occurred in approximately 34% of their cases.

The additional factor that would have been helpful would be a correlation of those thin melanoma excisions with the local skin recurrences (if any) to determine if there was any relationship between the extent of the surgical excision and the recurrence of the tumors.

GEORGE F. BALE, M.D.
Memphis, Tennessee

October 14, 1990

Dear Editor:

Dr. Seigler and I thank Dr. Bale for his letter regarding our article "Late Recurrence of Malignant Melanoma."

Approximately 25% of patients with complete histologic records had melanomas measuring less than 1 mm. These thin melanomas included 6 patients with extremity primaries, 10 patients with trunk primaries, and 5 patients with head/neck primary lesions. Interestingly only three of these patients experienced local recurrence. Most of these patients (11 of 21) had recurrence in the regional nodes and a large percentage (7 of 21) at distant sites, including lung, bone, and gastointestinal tract. The small number of patients (three) with thin melanomas who experienced local recurrence make analysis of the influence of margins of excision extremely difficult.

As indicated in Table 4, there were 17 patients with cutaneous melanomas who had local recurrence. These included 7 patients with extremity primaries, 7 patients trunk primaries, and 3 with head/neck primary lesions. These 17 local relapses occurred in the total population of 155 patients with cutaneous melanomas, for a total of 11% (rather than 34%). The Breslow thickness in this group of patients ranged from 0.45 mm to 3.35 mm. Again, only three of these patients had melanomas measuring less than 1 mm.

The issue of recurrent disease and survival in patients with thin melanomas (less than 0.76 mm) was evaluated for a group of 681 patients seen at the Duke University Melanoma Clinic. I would refer Dr. Bale to this paper by Slingluff et al. in a previous issue of the *Annals of Surgery* (1988; 208:150–161). In this analysis two clinical risk factors (axial primary site and male sex) and two histologic risk factors (Clark's level IV and severe histologic regression) were associated with an increased incidence of recurrence. Local skin recurrence was seen in 5% of patients and margins of excision were evaluated for this group of patients. Of those patients who experienced local recurrence, patients with margins of excision less than 1 cm had recurrence no sooner than those with wider margins, suggesting that narrow margins of excision (less than 1 cm) did not play a role in the risk of subsequent recurrence.

NANCY J. CROWLEY, M.D.
Durham, North Carolina

March 9, 1990

Dear Editor:

We read with interest the article entitled "Is Preoperative Angiography Useful in Patients with Periampullary Tumors?" by Dooley and associates (Ann Surg 1990; 211:649–655).

The authors evaluated the role of preoperative visceral angiography as a staging test adjunctive to computed tomography scan in patients with periampullary tumors. Thirteen of twenty-eight patients with positive angiographic evidence of vascular involvement were not explored and 6 of the remaining 15 who were explored had successful resection of the tumor. This false-positive rate of angiography (6 of 28) is quite high and disconcerting. The conclusion that all 17 patients with vascular occlusion as shown on angiography were unresectable is erroneous because only four of these were confirmed to be unresectable on exploration. But even if one believes that all of the 11 patients with total vascular occlusion were unresectable, the advantage of identifying this group of patients in 11 of 90 patients (12%) is offset by unwanted laparotomy in 14 of 90 patients (15%) in the angiogram-normal but unresectable group.

The data regarding peritoneal and liver spread is not available in 11 of 13 patients who were not explored (two had liver secondaries). Fifteen of the remaining seventy-nine patients had evidence of liver and peritoneal spread, which would have been amenable to detection by laparoscopy, a safe, cost-effective and accurate method.[1]

The question mark posed at the end of the title is very valid, and it should have been followed by an emphatic 'No.'

S. S. SIKORA, M.S.
V. K. KAPOOR, M.S.
Luchnow, India

Reference

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October 30, 1990

Dear Editor:

We thank Drs. Sikora and Kapoor for their interest in our study. We started with 90 patients who on the basis of computed tomography (CT) scan appeared to have resectable periampullary tumors. Visceral angiography demonstrated vascular occlusion in 11 of these 90 patients. Major vascular occlusion secondary to tumor is widely accepted as indicative of unresectability in periampullary tumors. Angiography is considered the definitive test for demonstrating vascular occlusion. After exploring 4 of these 11 patients and confirming that they were unresectable, we thought it was inappropriate and unwarranted thereafter to continue to explore such patients with major vascular occlusions. Seventeen patients had vascular encasement without occlusion demonstrated on angiography. At the time of laparotomy, encasement was confirmed in 13 patients. In two of these patients, however, the involved portal vein was resected and reconstructed. The remaining four patients at surgery were found to have no major vessel encasement and were resected. Thus the false-positive rate for the angiographic findings of both encasement and occlusion was 4 of 28 patients, or 14%. Although this rate is high, it does not obviate the value of angiography in preoperative staging of patients with periampullary tumors. We think the benefits of angiography are as follows: (1) avoiding needless laparotomy in patients with vessel occlusion; (2) alerting the surgeon to the possible need for major vascular resection and reconstruction in those patients with encasement; and (3) providing useful anatomic information to the surgeon concerning the hepatic arterial anatomy.

Other means of staging, such as laparoscopy, have been evaluated for patients with periampullary tumors. Although laparoscopy can identify superficial liver metastases and peritoneal implants, it is our belief that laparoscopy adds little to our current routine of staging by CT and angiography. In our series of 90 patients, six had peritoneal implants that would have been detectable at laparoscopy. Three of these patients had resectability excluded on the basis of visceral angiography. In addition at the time of exploration seven patients had resectability excluded by unsuspected liver metastases. Only four of these patients had superficial liver metastases that would have been detected by laparoscopy. The other three were deep-seated lesions. Therefore only 7 of our 90 patients would have benefited from laparoscopy in their staging evaluation before laparotomy. Using CT scan and viseral angiography, our overall resectability rate was 68%. This is the highest rate reported, and we think it justifies our approach.

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NANCY C. YUE, M.D.
ANTHONY C. VENBRUX, M.D.
Baltimore, Maryland

Dear Editor:

The paper by Dr. Souba et al.[1] published in *Annals of Surgery* is both interesting and valuable. The authors studied the effects of severe infection on gut glutamine metabolism in laboratory rats and in hospitalized patients. This study suggests that the gastrointestinal response to severe infection clearly is different from the response to surgical stress.

Intestinal glutamine consumption is increased in surgical stress despite a decrease in the circulating glutamine concentration. In sepsis, on the other hand, a marked reduction in gut glutamine use occurred with normal or increased arterial glutamine levels. The uptake of circulating glutamine by the gut occurs almost exclusively in the mucosal cells, where the content of the enzyme glutaminase is very high. In this study gut glutamine extraction decreased in septic patients and in endotoxin-treated rats. The authors attribute this phenomenom to an important compromise of the integrity of the gastrointestinal mucosa barrier by repeated exposure to systemic endotoxins.

Our group studied enterocyte amino acid concentrations in rats and we observed no changes in glutamine levels in starved or stressed animals compared to control.[2] In septic patients, however, we found significantly high plasma levels of glutamine with respect to reference values.[3] Freeysz et al.[4] also observed high plasma values of glutamine in a similar clinical situation.

The septic patients in our study received total parenteral nutrition with only 10% branched-chain amino acids. Furthermore it is accepted that in sepsis muscle glutamine values are low. The fact that our results showed high plasma glutamine levels may be explained by the decreased gut glutamine extraction described by Souba et al.

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October 16, 1990

Dear Editor:

We thank Dr. Planas and colleagues for their interest in our recent paper "The Effects of Sepsis and Endotoxemia on Gut Glutamine Metabolism."[1] We appreciate the observation by this group that the intestinal metabolic response to severe infection clearly is different from the response to pure surgical stress.

We would like to emphasize that the relationship between the decreased ability of the bowel to use circulating glutamine during sepsis and endotoxemia and the apparent breakdown in the gut mucosal barrier is, at this time, only an association. However the relationship between gut metabolism, structure, and function appears to be important because several studies showed that supplemental glutamine can influence gut morphology and function.[2–4]

Unlike patients undergoing elective abdominal surgery (who exhibit a decrease in the blood glutamine level), patients with early sepsis appear to have normal or slightly elevated blood glutamine levels. We agree with Dr. Planas and colleagues that this observation probably is due to a combination of a reduced uptake of glutamine by the bowel with an accelerated release of glutamine by skeletal muscle. The flux data is consistent with another organ of significant glutamine consumption during endotoxemia and preliminary data suggest that the liver becomes the principal organ of glutamine use during severe infection.[5]

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August 3, 1990

Dear Editor:

I read with interest a recent article "Reduction of Intimal Hyperplasia and Enhanced Reactivity of Experimental Vein Bypass Grafts with Verapamil Treatment."[1] However the method used to remove the vein was not according to established technique and thus prompts questions about the clinical implications of the study.

In a series of experiments, LoGerfo et al.[2-5] developed a technique for prevention of spasm and demonstrated with scanning electron micrographs essentially total preservation of endothelium in vein grafts and elimination of the intimal hyperplasia. The technique involves perivenous infiltration of a diluted papaverine solution, extreme gentleness in the dissection of the vein, early cannulation and distension with a Shiley vein distension set using warm papavarine (60 mg)/heparin (2000 U)/plasmalyte (500 mL) solution, and storing the vein in the distended state in the same solution at 4°C.

Baumann[6] and Sottiurai[7] in separate investigations confirmed the importance of papaverine, a balanced electrolyte solution, and prevention of overdistension of the vein segment. In the latest issue of *Vascular Surgery*, separate chapters, "In Situ Saphenous Vein Intimal Bypass" by Leather and Shah,[8] and "Translocated Autogenous Vein Grafts" by Cambria and Abbott[9] advocate this technique.

Thus, while it is encouraging that a newer agent such as verapamil holds promise for further reduction of intimal hyperplasia, before it can be considered a clinical advancement, the experimental protocol should use it in comparison to the above optimal method of vein preparation.

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October 24, 1990

Dear Editor:

It has long been recognized that meticulous attention to the preservation of the endothelium during harvest, storage, and transplantation of autologous veins may have beneficial effects on the long-term patency rates.[1] The literature cited by Dr. Paniszyn supports this concept. Of note, however, are the facts that the method advocated by Dr. Paniszyn differs from the most recently cited publication by Dr. LoGerfo[2] in that no albumin is included and that there are no available data from controlled trials examining the effect of this approach on short- and long-term graft patency. Currently available data on the optimal preservation of the endothelium in human saphenous veins remain controversial. In contrast to Dr. Paniszyn's comments, some authorities[3] advocate the use of crystalloid solutions and warm temperatures, while others[4] advocate the use of heparinized chilled autologous blood. The benefit of distention[3,5] as well as the use of papaverine by perivenous infiltration[3,6] and inclusion in the storage solution[7] is still debated. One of us (RLM) has found an increased incidence of wound complications due to bleeding in the graft bed when papaverine is infiltrated locally. As recently noted by Lawrie,[8] the use of papaverine or other relaxing agents such as nitroglycerin or calcium channel blockers needs to be investigated further.

In our experiments the veins were treated identically before transplantation under conditions that we recognize may not be optimal for the preservation of the endothelium. This model is advantageous in that it is well characterized in terms of the development of intimal hyperplasia and because the hyperplasia develops within a short experimental period. In this setting verapamil clearly reduces intimal hyperplasia. The use of such a model to study the pharmacologic manipulation of intimal hyperplasia development is essential for situations that do not allow the preservation of the endothelium. Therefore this type of study is important in clinical procedures that damage the endothelium, such as percutaneous angioplasty and the use of cardioplegic solutions.[9] In addition our study design, which permits the development of intimal hyperplasia in a relatively short time period, facilitates the investigation of the etiologic factors in the process—a major purpose of our investigations.

We agree with Dr. Paniszyn that whenever possible, conditions to maximize vein graft patency should be used. The current lack of consensus among clinical authorities on what the optimal harvest method should include suggests a need for further experimental work such as ours. Only with the demonstration of effectiveness in experimental models will we be able to design rational clinical trials of adjuvant pharmacologic treatment to improve long-term vein graft patency.

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September 20, 1990

Dear Editor:

We read with interest the report by Dr. Schoetz and associates from the Lahey Clinic, "Addition of Parenteral Cefoxitin to Regimen of Oral Antibiotics for Elective Colorectal Operations."[1] Our recent report, also supported by a grant from Merck, Sharp and Dohme, produced a different conclusion.[2] Both reports were prospective, randomized, double-blind studies conducted at single institutions, the Lahey Clinic and University Hospitals of Cleveland, respectively. Table 1 compares the two studies in reference to wound infection rates.

TABLE 1. Antibiotics in Colorectal Surgery

Study	Total Patients	% Wound Infection
Schoetz et al.[1]		
Oral antibiotics	96	14.6
Oral and IV	101	5.0
Stellato et al.[2]		
Oral antibiotics	44	6.8
Oral and IV	51	5.9
IV	51	3.9

IV, intravenous.

Although the study from the Lahey Clinic has twice as many patients as our study (discounting our intravenous-alone arm for which there is no comparable arm in the Lahey Clinic study), it must be noted that the infection rate in their oral and intravenous group is comparable to ours (5% *versus* 5.9%). In our study, however, the use of oral antibiotics alone also resulted in a low wound infection rate (6.8%), while Dr. Shoetz reports a rate of 14.6%. We concluded that intravenous antibiotics alone, oral antibiotics, or the combination of oral and intravenous antibiotics produced no significant difference in wound infection rates. Although increasing patient number usually provides more power (*i.e.*, a better ability to discern small treatment differences), the similar wound infection rates of their oral and intravenous antibiotic treatment arm with both of our groups (oral alone and oral and intravenous antibiotics) suggests that their observed difference is due to an increased incidence of wound infections in the oral antibiotic alone arm, not in our sample size. The explanation for their high infection rate is not apparent.

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November 1, 1990

Dear Editor:

We thank Dr. Stellato and colleagues for their letter questioning the differences between our study[1] and their own.[2] Certainly at first reading there is an apparent dichotomy in the conclusions. On careful review, however, there are some substantial differences that have contributed to the apparent discrepancy in the observed results. First the patients in our study were followed for up to 4 months from the time of discharge from the hospital. Consequently those individuals who developed a wound infection after discharge were included in our data. Second their definition of wound infection required visible pus in the wound or wounds from which a positive culture was obtained; our wound infection rate included those wounds that were clinically suspect and consequently opened, despite the fact that wound culture was not necessarily positive. Furthermore the presence of a pre-existing stoma was not an exclusion from our study group; in fact 32% of the total number of patients in our study had a stoma at the time of operation or had one created as part of the operative procedure compared with 10.3% of their total.

Finally, and most important, there are differences in patient populations, with, for example, 4.1% of their study group undergoing operation for inflammatory bowel disease compared with 27.4% in our study group. In short it is clear that the study groups are not equivalent in their composition.

Concerning statistical analysis, the 95% confidence interval in our oral antibiotic group with a 14.6% wound infection rate was 8.5% to 22.7% compared with their infection rate of 6.8% with a 95% confidence interval of 1.7% to 17.4%. A similar confidence interval for our combination oral and intravenous antibiotic infection rate of 5% was 1.8% to 10.6% compared to a confidence interval of 1.5% to 15.2% for their wound infection rate of 5.9%. Comparison of the wound infection rates between the two studies by contingency table analysis fails to approach $p < 0.05$ statistical significance with a probability value of 0.26 for oral antibiotics alone and 0.80 for the combination of oral and intravenous antibiotics. Confidence interval and contingency table values in this letter have been computed by an exact method, Miettinen's modification of the Fisher exact calculation,[3] to avoid computational errors inherent in chi-square testing of small samples and overestimation of probability by the classic Fisher exact computation.

We believe that the discordance in results of the two reports is derived from major differences in case selection, variations of range of diseases, and different criteria for diagnosis of infection. Our larger series reduces the range of confidence interval estimates. Perhaps a larger prospective study with wide spectra of colonic disease and procedures might define a special subset of patients who need parenteral antibiotics in addition to the regimen of mechanical cleansing and oral antibiotics.

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Long-term Results of Coronary Bypass Surgery

Analysis of 1698 Patients Followed 15 to 20 Years

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Between 1968 and 1975, 1698 patients underwent coronary artery bypass with autogenous saphenous vein and were followed for up to 20 years. Age at operation was 53.9 ± 8.4 years, and 1485 were men (88%). Angina was present in 1637 patients (96%). There was single-vessel disease in 306 patients (18%), double-vessel in 642 (38%), triple-vessel in 550 patients (32%) and left main stenosis in 200 (12%). Preoperative left ventricular quality was good in 1185 (70%), poor in 508 (30%), and unknown in five patients. Survival at 20 years was as follows: for single-vessel disease, 40%; double-vessel, 26%; triple-vessel, 20%; and left main, 25%. At 20 years of follow-up, 67% of surviving patients were asymptomatic and 26% were improved. Antianginal drug therapy consisted of nitrates in 49% of patients and beta-blockers in 26%. Graft patency at 0 to 5 years was 633 of 780 grafts (81%); at 6 to 10 years, 415 of 606 grafts (68%); at 11 to 15 years, 271 of 449 grafts (60%); and at 16 to 20 years, 65 of 140 grafts (46%). Coronary bypass reoperation was performed in 324 patients (19%) and survival of these patients was 62% compared to 37% for nonreoperation patients ($p < 0.05$). Cox analysis demonstrated that the major determinants of survival related to age at operation, extent of coronary disease, quality of ventricle, history of stroke, and preoperative congestive heart failure. At 20 years of follow-up of this early experience with coronary bypass, 76% of surviving patients had one or more patent grafts and the probability of freedom from reoperation was 0.62.

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THIS REPORT CONTAINS information regarding the long-term clinical and angiographic outcome of coronary bypass surgery in a series of patients who have been the subject of ongoing prospective studies. Previous reports documented the 5-year,[1-4] 10-year,[5] and 10- to 15-year[6,7] follow-up results. The aim of this study was to present data for the 15- to 20-year follow-up interval.

Materials and Methods

Between 1968 and 1975, coronary bypass surgery was performed by one surgeon (G. C. Morris) on 1698 patients at Baylor College of Medicine and The Methodist Hospital. The preoperative clinical characteristics of the patients are summarized in Table 1 and the angiographic data in Table 2. Ejection fraction data were not available for most patients from this early experience, and therefore left ventricular function was defined as good if the left ventricular end-diastolic pressure was less than or equal to 15 mmHg and there was no akinetic or aneurysmal segment present on left ventriculography. Left ventricular function was considered to be poor if the end-diastolic pressure was more than 15 mmHg or there was an akinetic or aneurysmal segment. Previously we reported the results of an analysis of another group of 447 patients from our coronary database for whom preoperative ejection fraction, end-diastolic pressure, and the results of left ventriculography were available.[6] In the 239 patients classified as having good ventricular function, the mean ejection fraction was 60% ± 1.25% (± standard error). In the 208 patients classified as having poor function, the mean ejection fraction was 45% ± 0.9%. Thus, although not ideal, the classification used in this study did define two groups of patients with different prognoses.

The surgical procedures were all performed using a standardized technique. Autogenous long saphenous vein from the thigh was used for all bypasses. The veins were prepared by distension with room-temperature normal saline and then stored in saline at room temperature. Patients were placed on normothermic crystalloid prime cardiopulmonary bypass. The distal anastomoses were performed during a single period of normothermic aortic cross-clamping. The proximal anastomoses were performed during a period of partial aortic occlusion, with the empty beating heart supported by full-flow cardiopulmonary bypass. No antiplatelet agents were employed after operation.

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TABLE 1. *Clinical Characteristics Before Operation of 1698 Patients Who Underwent Saphenous Vein Coronary Bypass*

Parameter	Value
Age (yrs)	53.9 ± 8.4 (SD)
Sex	
Male	1485 (87%)
Female	213 (13%)
Angina pectoris	1637 (96%)
History of myocardial infarction	1030 (61%)
History of congestive failure	195 (11%)
History of stroke	47 (3%)
Obesity	606 (36%)
Smoking	1023 (60%)
Diabetes	255 (15%)
History of hyperlipidemia	985 (58%)
Blood pressure	
Systolic	136.9 ± 20.9 mmHg
Diastolic	82.8 ± 11.5 mmHg
Plasma cholesterol	246 ± 53 mg/dL
Plasma triglyceride	222 ± 138 mg/dL
Serum glucose	98 ± 41 mg/dL
Digoxin use	314 (18%)
Vasodilator use	1352 (80%)
Propranalol use	324 (19%)
Diuretic use	256 (15%)
Antiarrhythmic use	140 (8%)
Antihypertensive use	324 (19%)

After hospital discharge, follow-up of clinical status was assessed prospectively for all patients at regular intervals using a standardized questionnaire and supplemented by telephone inquiries to patients and their physicians.

Postoperative cardiac catheterization was performed 1219 times in 818 of the 1698 patients. Results of these studies were also recorded on standardized data sheets. Vein grafts were classified as either patent or occluded. A vein graft was considered patent if it provided a communication of any size between the ascending aorta and the distal coronary artery. Patent grafts were further classified as either normal if there was no luminal irregularity causing greater than 20% stenosis or stenotic if there was greater than 20% stenosis.

The data from this study were entered into a custom database system written in MUMPS (Intersystems Inc. M/SQL [V5B.0-90-06B] resident on a DEC VAX/750 running VAX/VMS V5.3). The associations among discrete variables were analyzed by two-way contingency table analyses, and the statistical significance was calculated by the Pearson chi square test. The differences among groups were determined by analysis of variance for continuous variables and nonparametric methods for nominal data. Univariate analyses were performed also by means of Kaplan–Meier curves to estimate the influence of variables on the time-related probability of freedom from death or reoperation. The stepwise proportional hazards regression model of Cox was used to evaluate the influence of covariate factors on the survival interval. The BMDP Statistical Software 1990 (VAX/VMS) (BMDP Statistical Software Inc., Los Angeles, CA) package was used for all statistical computation except Kaplan–Meier survival plots, which were generated by a custom routine validated against BMDP. Expected survival of these patients was calculated from the mortality rates presented in the 1970 United States Census for an age- and sex-adjusted population.[8–11]

Results

A total of 3205 separate grafts were performed in 1698 patients, for a mean of 1.9 ± 0.6 grafts per patient. This resulted in the presence of residual disease after surgery in 471 of 1392 (33.8%) of the patients with multivessel coronary disease. Residual disease was considered to be present when one or more vessels with greater than 50% stenosis received no graft.

Perioperative deaths occurred in 85 patients (5%) within 30 days of operation.

Follow-up was 92.2% complete at 20 years. The mean follow-up interval was 15.2 ± 4.2 years for survivors, and the mean interval from operation to death in nonsurvivors was 8.6 ± 5.2 years.

Symptom status, work status, and current medication usage are summarized in Table 3. The results of evaluation of graft patency according to individual grafts are shown in Table 4. Overall graft patency in the 16- to 20-year interval was 46%. The numbers of patients with one or more patent grafts are shown in Table 5. Of the patients followed 16 to 20 years, 76% had one or more patent grafts. Analysis of the influence of various levels of cholesterol and triglycerides on vein graft patency were performed ($p > 0.05$ for differences in 20-year patency at different triglyceride levels). The triglyceride level did not influence graft patency. Patients with total cholesterol levels greater than 280 mg/dL had significantly lower graft patency in the 10- to 20-year interval (Fig. 1).

A total of 1016 deaths (60%) have occurred. This includes perioperative mortality. For sample of the general US population of 1970 adjusted for age and sex distribution,[11] 838 deaths (49.4%) would have been expected over the 20-year interval. Thus the observed to expected mortality ratio was 1.2 over the 20-year interval, an excess

TABLE 2. *Preoperative Coronary Angiographic and Left Ventriculographic Findings in 1698 Patients*

Factor	No. Patients (%)
Number of stenotic coronary arteries	
One artery	306 (18)
Two arteries	642 (38)
Three or four arteries	550 (32)
Left main artery	200 (12)
Quality of left ventricle	
Good	1185 (70)
Poor	508 (30)
Unknown	5 (0.3)

TABLE 3. *Results of Clinical Follow-Up at 5-Year Intervals of the 1698 Patients*

	Interval			
Factor	0–5 Years	6–10 Years	11–15 Years	16–20 Years
Relief of angina				
No. of responses	576	761	676	332
Asymptomatic	328 (57%)	406 (53%)	365 (54%)	221 (67%)
Improved	206 (36%)	286 (38%)	240 (36%)	86 (26%)
Same	34 (6%)	52 (7%)	38 (6%)	17 (5%)
Worse	8 (1%)	17 (2%)	33 (5%)	8 (2%)
Symptoms of heart failure	34/538 (6%)	70/658 (11%)	133/680 (20%)	103/334 (31%)
Work status				
No. of responses	531	643	660	321
Same	255 (48%)	248 (39%)	245 (37%)	82 (26%)
More	20 (4%)	41 (6%)	80 (12%)	17 (5%)
Less	64 (12%)	107 (17%)	192 (29%)	114 (35%)
None	192 (36%)	247 (38%)	143 (22%)	108 (34%)
Medication use (positive response/total response)				
Digoxin	112/516 (22%)	168/646 (26%)	159/680 (23%)	56/322 (17%)
Vasodilator	113/512 (23%)	259/647 (40%)	298/685 (44%)	161/329 (49%)
Beta blocker	117/513 (23%)	213/640 (33%)	219/680 (32%)	83/322 (26%)
Antiarrhythmic	46/512 (9%)	82/637 (13%)	84/672 (13%)	48/321 (15%)
Oral hypoglycemic	1/3 (33%)	4/4 (100%)	7/121 (6%)	20/302 (7%)

mortality rate of about 20%. Cardiac causes of death predominated, accounting for 513 of all the 1016 deaths (50.5%). Cardiac deaths occurred from recurrent myocardial infarction (260 patients), progressive congestive heart failure (136 patients), or from arrhythmias (117 patients). Cancer accounted for 89 deaths and stroke for 51 deaths. The cause of death could not be determined in 199 patients. A large variety of other causes were responsible for the remaining deaths.

The results of Kaplan–Meier analysis of the influence of sex on survival probability is shown in Figure 2. Survival was similar for men and women. The influence of the number of vessels diseased before operation on survival is shown in Figure 3. The influence of quality of preoperative ventricular function on survival is shown in Figure 4. Figures 5 and 6 illustrate survival probability according to the simultaneous influence of quality of ventricle and the number of vessels diseased.

Kaplan–Meier analyses of the influence of plasma total cholesterol, triglycerides, diabetes mellitus, and systolic blood pressure on 20-year survival probabilities demonstrated that neither the total cholesterol nor the triglyceride levels were predictive of survival (Figs. 7 and 8), whereas the presence of diabetes or a systolic blood pressure of at least 161 mmHg were associated with reduced survival (Figs. 9 and 10). A more detailed analysis of the influence of diabetes mellitus on 10- to 15-year survival rates in 212 of these patients has been reported previously.[7] The age at operation was also a significant predictor.

The survival of the 471 patients with multivessel disease who had residual disease was compared with the remaining 911 patients who received a graft to each major coronary artery with a significant stenosis and thus had no residual disease. The survivals of patients with double-vessel disease and either no or one residual lesion are shown in Figure 11. Long-term survival was significantly lower in the presence of a residual lesion ($p < 0.05$).

The survival probabilities of patients with triple-vessel

TABLE 4. *Results of 1975 Graft Evaluations from 1219 Studies in 818 Patients*

Years (No. of Patients Cathed)	RCA	LAD	LCA	DIAG	Total
0–5 (418)					
No. patent/no. studied	214/271 (79%)	304/362 (84%)	99/122 (81%)	16/24 (64%)	633/780 (81%)
6–10 (333)					
No. patent/no. studied	138/207 (67%)	221/291 (76%)	54/96 (56%)	2/12 (17%)	415/606 (68%)
11–15 (236)					
No. patent/no. studied	86/156 (55%)	141/204 (69%)	39/79 (49%)	5/10 (50%)	271/449 (60%)
16–20 (232)					
No. patent/no. studied	21/42 (50%)	33/56 (59%)	11/26 (42%)	—	65/140 (46%)

Cathed, catheterized; RCA, right coronary artery; LAD, left anterior descending coronary artery; LCA, left circumflex coronary artery; DIAG, diagonal.

TABLE 5. *Analysis of the 818 Patients Who Underwent Postoperative Vein Graft Study According to the Presence or Absence of One or More Patent Grafts*

Time to Most Recent Catheterization	At Least 1 Patent Graft	No Patent Grafts	Total Patients
≤31 days	37 (95%)	2 (5%)	39
1 month to 5 years	206 (88%)	29 (12%)	235
6–10 years	206 (79%)	56 (21%)	262
11–15 years	172 (78%)	48 (22%)	220
16–20 years	49 (79%)	13 (21%)	62
Total patients studied	670 (82%)	148 (18%)	818

disease are presented according to the extent of residual disease (Fig. 12). Both one and two residual lesions had a significant impact on late survival ($p < 0.005$).

Coronary bypass reoperation was performed in 324 (19%) of patients at a mean interval of 9.5 ± years from initial operation. Perioperative mortality was 11.4% (37 patients). The probability of freedom from reoperation for all patients and the survival of the 324 patients after reoperation are shown in Figures 13 and 14. Reoperation was required for residual disease in 79 patients (27%) and progression of disease or graft failure in 244 patients (73%). The influence of reoperation on subsequent survival probability is shown in Figure 13, which provides a comparison of overall survival of the 1698 patients with the survival of all reoperated patients from the time of their first coronary bypass. The survival of the reoperated patients also is plotted from the time of their reoperation. Figure 14 illustrates the probability of freedom from coronary bypass reoperation for the 1698 patients over the 20-year interval. At 10 years the probability of freedom from reoperation was 0.87; at 15 years, 0.72; and at 20 years, 0.62.

Cox regression analysis was performed to evaluate the influence of preoperative and intraoperative variables on

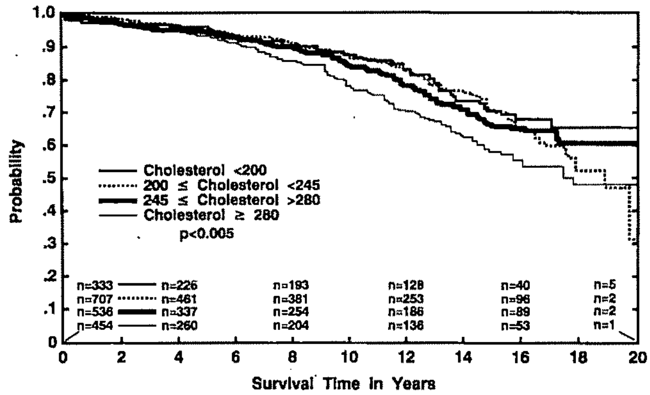

FIG. 1. Influence of various levels of total plasma cholesterol on the 20-year patency of saphenous vein grafts analyzed by the Kaplan-Meier technique. The number of patent grafts available for analysis at each interval are shown.

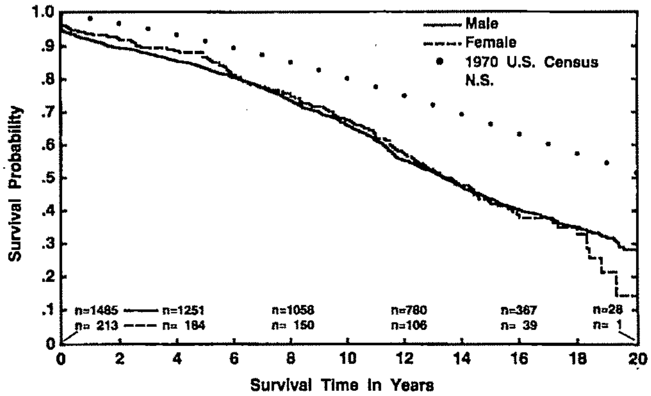

FIG. 2. Comparison of the survival probabilities (Kaplan-Meier) of 1485 men and 213 women after coronary bypass surgery. Survival was similar at all intervals for men and women. ($p > 0.05$ for differences). The expected survival for an age and sex adjusted sample of the general population is shown for comparison on this and subsequent figures. (See text for details of methods used to derive this population.)

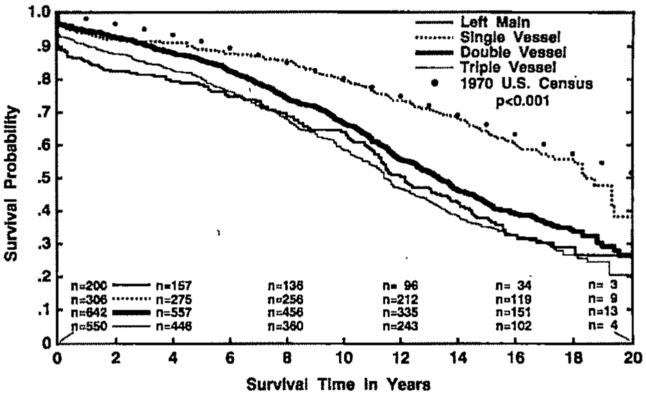

FIG. 3. Survival probabilities of 1698 patients according to the extent of coronary disease before operation.

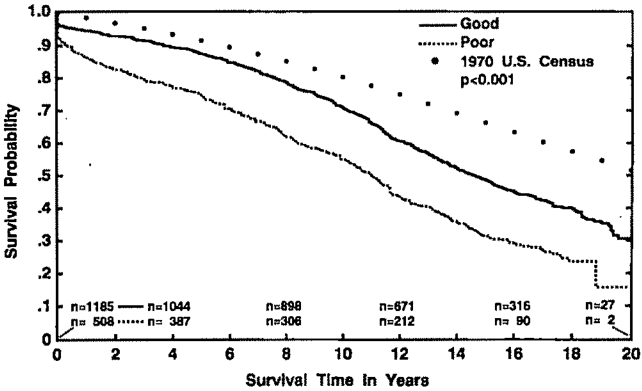

FIG. 4. Survival probabilities of 1698 patients according to the quality of left ventricular function before operation. (See text for definitions of good and poor left ventricular function.)

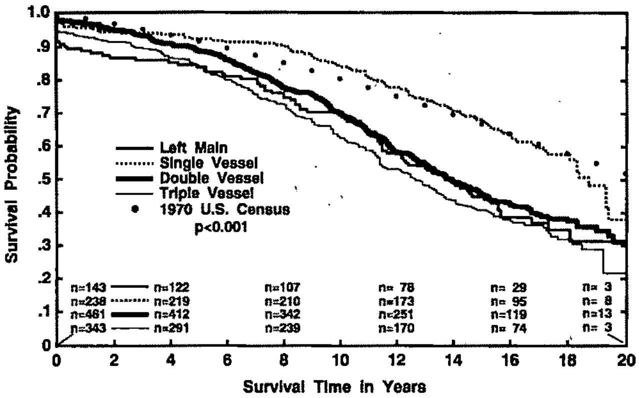

FIG. 5. Survival probabilities of 1185 patients with good left ventricular function according to the number of vessels diseased.

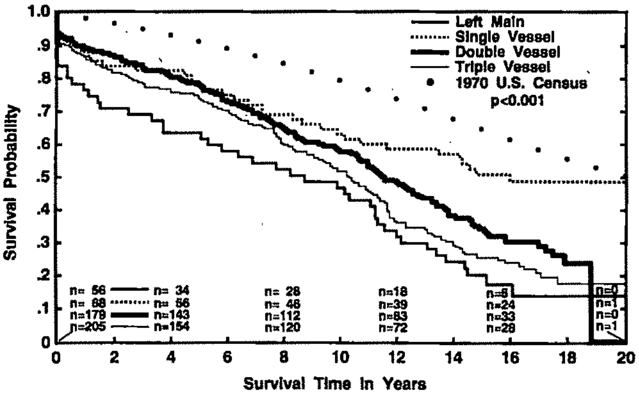

FIG. 6. Survival probabilities of 508 patients with poor left ventricular function according to the number of vessels diseased.

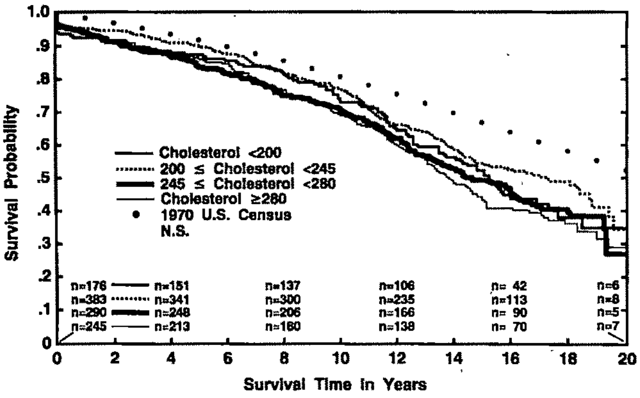

FIG. 7. Influence of total cholesterol (mg/dL) on the 20-year survival of 1094 patients for whom cholesterol data was available. There were no significant differences in survival (p > 0.05).

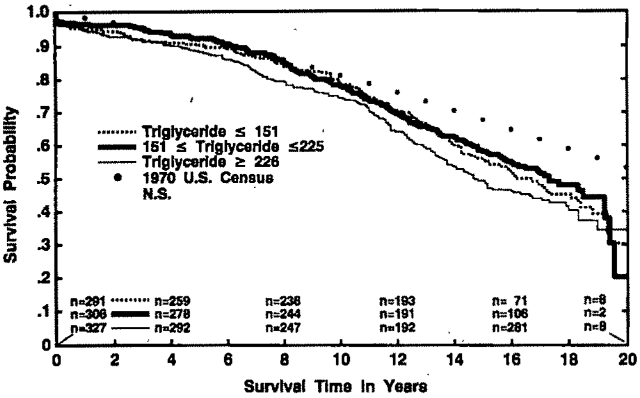

FIG. 8. Influence of the plasma triglyceride level on 20-year survival. Triglyceride levels are in mg/dL. There were no significant differences in survival probabilities.

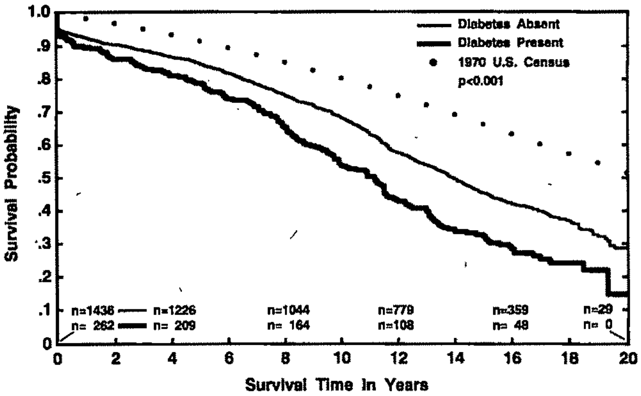

FIG. 9. Influence of diabetes mellitus on the 20-year survival probability of 1698 patients, of whom 262 were diabetic.

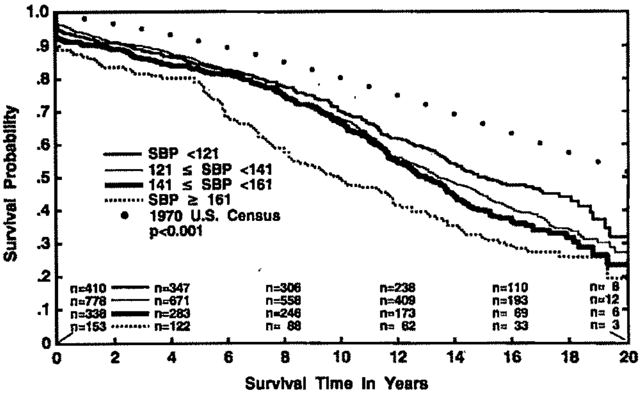

FIG. 10. Influence of level of systolic blood pressure (SBP) in mmHg before operation on 20-year survival probability.

overall survival (Table 6). Many variables had some independent predictive value, in part due to the large number of patient-years available for analysis. The most important variables, however, related to the extent of coronary disease and factors associated with the quality of left ventricular function. The risk factors of age, systolic hypertension, diabetes mellitus, and a history of preoperative stroke were also important predictors.

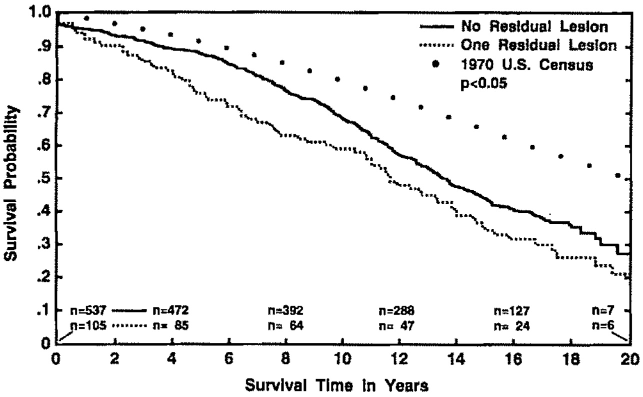

FIG. 11. Survival probabilities of patients with double vessel disease according to the presence or absence of a residual lesion.

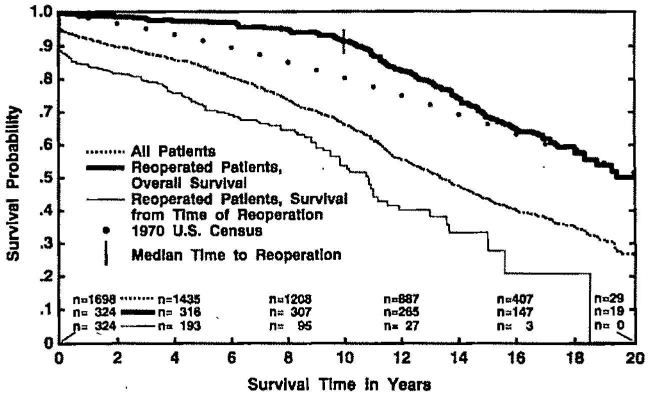

FIG. 13. Survival probability of 324 patients who underwent coronary reoperation. A comparison is provided for both survival from the first coronary bypass operation and for survival from the time of reoperation.

A total of 918 peripheral vascular procedures were performed on 638 (38%) patients during the follow-up interval.

Discussion

This early experience with coronary bypass surgery differs in several notable respects from current practice. Most patients were operated on before the availability of beta-blocking agents, and none were treated before operation with calcium channel-blocking agents. These factors, combined with anesthetic techniques that were still evolving, led to significant problems with hemodynamic instability before institution of cardiopulmonary bypass in many of the higher-risk patients.

There were a small number of grafts performed per patient (1.9) compared with our current practice of performing three to four grafts per patient in most cases of multivessel disease. The saphenous vein was used exclusively, whereas now at least one internal mammary bypass is performed in more than 80% of patients.

No hypothermic or cardioplegic myocardial protection was used. Although this had little impact on the results in patients with good preoperative left ventricular function, patients with severely impaired ventricles and multivessel coronary disease experienced significant perioperative mortality from left ventricular dysfunction.

Despite these problems, most of the patients have done well over the 15- to 20-year follow-up interval. Analysis of the impact of the coronary bypass on clinical status and survival has become more complicated as the follow-up interval has lengthened, because most surviving patients are now older than 70 years and, like the rest of their peer group, have retired and become more sedentary. Furthermore to survive over such a long follow-up interval, it is likely that, in the 15- to 20-year survivors, characteristics of their coronary disease and graft function have provided them with this outcome, in contrast to the fate of the nonsurviving patients. Thus it is difficult to assess how many of the changes in activity levels documented in Table 3 are due to self-selection for survival, aging alone, and how many are due to their coronary disease.

Despite these problems relief of symptoms, as described

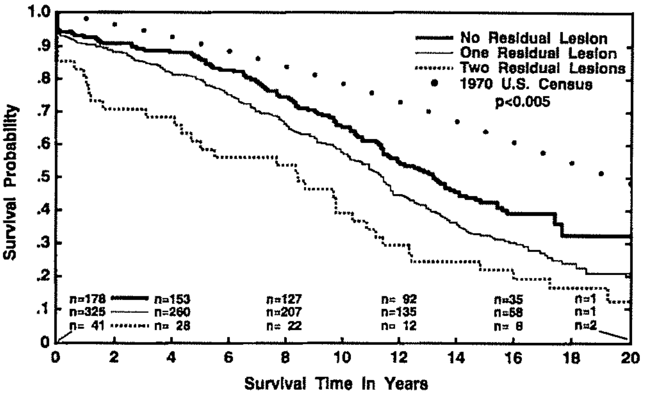

FIG. 12. Survival probabilities of patients with triple vessel disease according to whether one or two residual lesions were present.

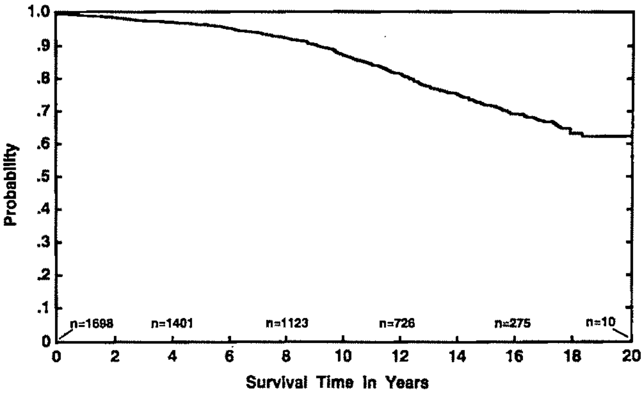

FIG. 14. Probability of freedom from coronary bypass reoperation for the 1698 patients over a 20-year period.

TABLE 6. *Results of Cox Regression Analysis for Factors Predictive of Overall Mortality Rate*

Variable	Beta	SE (B)	Level	RR (95% CI)	χ^2	p Value
Left main disease	0.6585	0.1264	Absent	1.0	27.15	<0.0001
			Present	1.9 (1.5, 2.5)		
Age at operation	0.0209	0.0041	0	1.0		
			Per year	1.02 (1.01, 1.03)	25.43	<0.0001
Systolic blood pressure	0.0066	0.0015	0	1.0		
			Per mmHg	1.007 (1.003, 1.010)	20.48	<0.0001
Number of vessels diseased			1 or less	1.0		
	0.3803	0.1049	2 vessels	1.5 (1.2, 1.8)	20.17	<0.0001
	0.5199	0.1208	3 or more	1.7 (1.3, 2.1)		
Preoperative CHF	0.3984	0.0995	Absent	1.0		
			Present	1.5 (1.2, 1.8)	16.04	0.0001
Diabetes	0.3347	0.0841	Absent	1.0	15.85	0.0001
			Present	1.4 (1.2, 1.6)		
Preoperative stroke	0.6616	0.1680	Absent	1.0	15.51	0.0001
			Present	1.9 (1.4, 2.7)		
Preoperative myocardial infarction	0.2494	0.0707	Absent	1.0	12.46	0.0004
			Present	1.3 (1.1, 1.5)		
Ventricular quality	0.2499	0.0715	Good	1.0	12.22	0.0005
			Poor	1.3 (1.1, 1.5)		
Preoperative digoxin	0.2817	0.0871	Absent	1.0	10.45	0.0012
			Present	1.3 (1.1, 1.6)		
Assoc valve surgery	1.6296	0.5809	Absent	1.0	7.87	0.0050
			Present	5.1 (1.6, 15.9)		
Isolated CABG	−0.4569	0.1666	No	1.0	7.52	0.0061
			Yes	0.63 (0.46, 0.88)		
Preoperative diuretic use	0.2459	0.0908	Absent	1.0	7.34	0.0067
			Present	1.3 (1.1, 1.5)		
Residual disease	0.1702	0.0847	Absent	1.0	4.04	0.0446
			Present	1.2 (1.0, 1.4)		

B, beta; SE (B), standard error; RR, relative risk; CI, confidence interval; χ^2, chi square; CHF, congestive heart failure; Assoc, associated; CABG, coronary artery bypass graft operation.

by the patients, has been persistently good. Freedom from angina has been well maintained, but at the same time there has been a progressive increase in the use of various forms of coronary vasodilators, including calcium channel-blocking agents. The most important change in symptoms has been the significant increase in the number of patients reporting symptoms of congestive heart failure. Whether this is due to true congestive heart failure secondary to progressive deterioration of left ventricular function or is a manifestation of the left ventricular hypertrophy and diastolic dysfunction seen in coronary disease could not be determined in this study.

We have not observed the marked deterioration in symptom relief reported by Campeau et al.[12] of 3.7% per annum. Our results are similar to those of Schaff et al.[13]

There are few reports of long-term survival data with which to make comparisons with our own study. In the randomized European Coronary Surgery Study[14] the overall survival at 12 years of follow-up was 70.6% ± 5.8% for surgically treated and 66.7% ± 5.3% for medically treated patients. This study was restricted to patients with reasonably good preoperative left ventricular function. Our group of patients with good left ventricular function achieved a survival rate of 60.6% at 12 years.

The Veterans Administration Coronary Artery Bypass Cooperative Study Group[15] reported that, at a follow-up interval of 11 years, the survival probability for single-vessel disease treated medically was 0.65 and for surgically treated patients was 0.70. At 11 years the survival probability of our surgically treated patients with single-vessel disease was 0.76. For double-vessel disease our survival was 0.61 at 11 years, compared with a VA medical rate of 0.69 and operative rate of 0.55. For triple-vessel disease, the VA survival probability was 0.50 for medical and 0.56 for surgical treatment, compared with our surgical result of 0.54.

Proudfit et al.[16] reported on the 15-year survival of a medically treated 'surgical candidate' group of 386 patients. The 15-year survival rates were, for single-vessel disease, 57% to 61%; double-vessel disease, 23% to 30%; and triple-vessel disease, 17% to 30%. The corresponding figures at 15 years for our surgical patients are 0.63, 0.42, and 0.35.

Proudfit also noted that the main predictors of 15-year survival identified by Cox regression analysis were the presence of two- or three-vessel disease, hypertension, symptoms for more than 5 years, abnormal electrocardiographic (ECG) findings, evidence of peripheral vascular disease, and an end-diastolic pressure greater than 30 mmHg.

The deleterious influence of residual disease was recognized early in our experience with coronary bypass.[1,2,4]

The adverse influence of failure to revascularize all major graftable vessels has continued through the 15- to 20-year interval. As shown in Figures 11 and 12, the 15-year survival probability for patients with completely revascularized double-vessel disease was 0.43, compared with 0.34 for incompletely revascularized patients. For triple-vessel disease the effect was even greater, with a survival probability of 0.42 for no residual lesion, 0.32 for one residual lesion, and 0.22 for two residual lesions.

Other authors have reported similar findings with regard to the adverse influence of residual disease on survival.[17–24] An additional benefit of more complete revascularization has been improved relief of angina and exercise tolerance after surgery.[25–27]

These long-term data continue to demonstrate that it is important to ensure that all stenosed major epicardial coronary arteries receive a bypass graft. Currently the average number of grafts placed is 3.4 per patient.

The other factor critically important to the long-term success of the operation is the behavior of the saphenous vein grafts. In our own experience we have documented a steady rate of attrition of graft patency of 2% to 3% a year (Table 4).[1–7,28,29]

Despite this attrition and the small number of grafts performed in each patient, 79% of patients (Table 5) had at least one patent graft in the 16- to 20-year interval.

In earlier reports we documented the occurrence of intimal proliferation[30] and later, atherosclerosis[31] in the saphenous vein grafts. Whereas progression of coronary disease appears to have had a minor role in vein graft occlusion in our experience,[1,6] vein graft atherosclerosis now has emerged as the major threat to the long-term patency of the vein grafts. This is consistent with data from other long-term studies[32–34] showing progressive degeneration of vein grafts with time.

The cause of these changes remain unknown. Some authors consider hyperlipidemia-induced lipid uptake by the vein wall to be the dominant event.[33] Our own data has consistently failed to demonstrate significant differences in the total cholesterol, triglyceride, or lipoprotein levels of patients with normal or abnormal grafts late after operation, except in patients with very severe hypercholesterolemia.[29,31]

We believe that intraoperative manipulation of the saphenous veins may cause trauma to the intima and media that leads to changes ultimately culminating in the late onset of graft atherosclerosis. Our studies on human saphenous vein suggest that vein preparation with saline solution should be abandoned and replaced with a balanced salt solution containing albumin.[35,36] Our data are consistent with the results of many other studies, which we recently reviewed at length.[36]

Initially in this experience, reoperation was required for correction of residual disease. Subsequently the major cause of reoperation has been vein graft failure. The reoperation rate was 1% per annum up to 9 years of follow-up, but thereafter increased to 2.5% per annum. However this rate has remained stable during the 10- to 20-year interval. Similar rates of reoperation have been noted for this same interval by other authors.[37] A substantial reduction in the reoperation rate to less than 0.5% per annum has been noted in more recent experience. As reported by others, our patients after reoperation had long-term survival rates comparable to other nonreoperated patients.[38,39]

It was of interest to note that age at operation, diabetes mellitus, systolic hypertension, and a history of stroke all continued to be significant predictors of overall survival. Over a 20-year period, it is evident that patients aged 60 to 70 years will ultimately have a survival disadvantage compared with patients aged 50 years. As we have reported previously,[7] diabetic patients experienced excess mortality from cardiac, renal, and stroke events. The role of systolic hypertension as a risk factor for cardiovascular mortality has received increasing attention in recent years.[40–42] In this study it was a relatively powerful independent predictor of death.

Notably absent as a risk factor predictive of death was the total serum cholesterol level. These findings are consistent with those of the Framingham study, which showed no association of level of cholesterol with mortality for men over 50 years of age.[43]

Changes in practices that should lead to enhanced long-term results among patients currently undergoing coronary bypass surgery include improved preoperative and intraoperative patient stabilization, better vein graft preparation techniques, and the liberal use of one or both internal mammary arteries. The use of perioperative and long-term aspirin therapy has favorably affected early and intermediate graft function and has important experimentally demonstrated effects on vein graft lipid metabolism.

The results of this study further emphasize the need for sustained intensive medical supervision of these patients and treatment of all controllable risk factors. The role of intensive lipid lowering in these patients is not yet established.

The significant proportion of patients dying from arrhythmias suggests that greater attention needs to be given to the management of patients who manifest serious arrhythmias in the preoperative or perioperative intervals or during the long-term follow-up interval. Such patients may benefit from more intensive evaluation, including electrophysiology studies.

Given the foregoing, it is highly probable that patients now undergoing coronary bypass will have more favorable long-term results than those of the 1698 patients in this study.

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DISCUSSIONS

DR. ROBERT JONES (Durham, North Carolina): For most patients, coronary artery disease is a chronic phenomenon. It may be punctuated by sudden untoward events. Therefore it's appropriate to follow these patients for many years, such as these data showing medically treated patients at Duke University Medical Center during the same era as the data demonstrated to you so nicely by the Baylor group.

These data represent freedom from cardiac death, not total death, but illustrate that about one half of the people treated medically during a period of 18 years have died as a result of their coronary disease. In segmenting these medically treated patients by the year they were catheterized and entered into medical treatment, we notice an apparent improvement in those medically treated in more recent time intervals, the last two intervals from 1978 to the present being roughly equivalent.

However, with more careful evaluation of the baseline characteristics that control risk in these medically treated patients, of which there are four, the apparent improvement was due to the lower baseline risk of the medically treated population. And that was because we were more effective in recognizing the high-risk patient, not treating medically, and placing him in the surgical population. Fortunately, during this interval, we were consistently improving surgical results so that our surgical mortality rate continued to decrease even as we absorbed these higher-risk patients.

On this slide is shown the relative hazard of being treated medically or surgically, with this being equal hazard in the middle at one, benefit on your left, and surgery actually being harmful on your right, in the patient's cohort receiving either medical or surgical treatment in 1970, 1977, or 1984.

In 1970, surgery was only helping those patients with the most severe form of disease anatomically, those with left main. By 1977 we were helping the three-vessel patients. And by 1984 we were helping all patients with at least two-vessel disease and, perhaps, even helping some patients with single-vessel disease.

And we've seen continued improvement in surgical outcome since 1984, particularly associated with increased use of the internal mammary artery graft.

The final piece of data calculates, based on the baseline variables of patients, the relative improvement in surgical treatment compared to medical outcome, starting with patients with very low risk on the left and continuing to patients whose baseline characteristics that place them at very high risk on the right.

At every level of risk there is an incremental improvement in survival rate at 5 years in the surgically treated patients.

There is a price to pay in increased operative risk to achieve this greater 5-year survival.

The patients who are higher risk treated medically have a better outcome if treated surgically, but you must pay a higher risk of operative mortality. However we could define no population in which the risk of surgery began to approach the risk of the medically treated population.

Certainly, somewhere in the world, there must be a patient with too much heart disease to benefit from operation, but we've not yet been able to define this individual. And, in fact, our practice has tended toward operating on those individuals with greater risk treated medically and not operating on the patients with more minimal risk.

I have one question that I would like to address to Dr. Lawrie. What criteria is currently used at the Baylor medical institutions for turning down coronary surgery to patients because of high risk? Are patients turned down because they are too sick for coronary bypass grafting?

DR. JOSEPH MCLAUGHLIN (Baltimore, Maryland): Dr. Lawrie that was a marvelous series that you presented. When I looked at the abstract a few weeks ago, I was struck by the difference in current procedures compared to those performed 20 years ago.

So I asked my secretary to get us a computer readout of procedures we are doing now. We've operated on 1300 patients during the last 3 years. Your average age was 54 years. In our group the average age was 64 years. And 10% of the patients were older than 75 years.

Twelve per cent of your patients were female; 29% of our patients are female. That's an important figure because women have a much higher mortality rate—a consistent finding around the country—than do the male patients.

Thirty-two per cent of your patients had triple-vessel disease. I believe that's the right figure. Seventy-six per cent of our patients had either three or four grafts. Only 5% of our patients at the present time have single-vessel coronary bypasses, and these were virtually all emergencies in the last few years following failed PTCAs.

Morbidity is also worse. This goes with what Dr. Jones has noted. We defined hypertension, carotid disease, COPD, and diabetes as comorbid factors. One can look at whatever factors you like, but these seem to be the most important ones.

Thirty-two per cent of our patients are hypertensive, 23% were diabetic, rates that are much higher than we saw years ago. And if we add those four together, 65% of our patients have comorbid factors at the present time.

Which then brings us to a mortality rate. Your rate was very good for that period of time. I believe it was about 3%. Our rate is 4% for this group of patients.

And that's interesting because 62% of our patients are either operated on emergently or urgently. These are significant numbers. The mortality rate varies from about 1% to about 17% for those patients who are operated on out of the intensive care unit, who are older than 65 years.

I think it's an entirely different ball game today, 20 years later. And I wonder—and I guess the question or the speculation I would ask of you is, what do you expect to see in the next 20 years with this kind of patient? I assume your patients are the same as ours.

And then, what are you going to tell the cardiologist when you are dealing with this group?

What do you expect in the long term? And, most importantly, what do you tell your patients when dealing with this kind of thing?

And, finally, how are we going to deal with it in a political sense when quality assurance groups are looking at us and saying, you know, your mortality rate is higher than it was 10 years ago, and indeed it is?

DR. GILBERT CAMPBELL (Little Rock, Arkansas): The influence of hyperlipidemia in your study is at complete variance with a recent report that we participated in that appeared in the *New England Journal of Medicine,* in the October 4, 1990 issue. I'm alluding to the Program on the Surgical Control of Hyperlipidemia (POSCH).

This study involved some 838 patients, one half of whom were controls; the other half had the distal ileal bypass to lower cholesterol. This procedure is a proved effective means to lower cholesterol in the long term. All patients had a documented myocardial infarction before entry into the study and before randomization. All of them had the usual treatment with diet and/or drugs.

Cardiovascular procedures, be it angioplasty, coronary artery bypass, peripheral vascular procedures, and so forth, were performed twice as frequently in those patients who were in the control group compared to those patients who had their hyperlipidemia significantly decreased by virtue of the distal ileal bypass (Buchwald procedure).

The Program on the Surgical Control of Hyperlipidemias was set up approximately 20 years ago. At that time, distal ileal bypass was the best and most predictable means to lower cholesterol significantly. Our study was a prospective, unifactorial study concentrating on lipid levels, whereas your study was retrospective and multifactorial tending to mask the importance of hyperlipidemia on atherogenesis.

DR. GERALD M. LAWRIE (Closing discussion): I think we're all very familiar with the excellent work from the Duke Data Registry.

I had a slide of our cardiac death rate after surgery, and it was identical to the general United States population. So our surgical patients had about a 10% to 15% advantage over the medically treated patients in terms of cardiac death in our series.

The issue of risk of operation is extremely important. It gets back to the whole issue of patient selection. I think we can only make those decisions based on data that gives us some feel for how much benefit the patient can get both early and later after operation compared with continuation of other treatments, which, of course, these days not only include medicine but also angioplasty.

And it will be very interesting to see some of these randomized studies of angioplasty coming out. I think we're going to be very pleasantly surprised by the results.

In terms of who is sickest, I think with the use of endarterectomy, patients who really need these operations can undergo them in almost all cases from a technical point of view. The two variables that we constantly are concerned about are, first, the risk of stroke, and second, bad cerebrovascular disease in our elderly patients.

And the other group of those patients with severe congestive heart failure, very poor ventricles, and absence of angina, and in our experience, have done quite poorly.

We get them through the surgery, and then 6, 12, 18 months later they die of congestive heart failure. And now that transplants are available, I think they may be better treated another way.

But I think Dr. Jones has continued to raise a very important issue, which is that fixation should not be associated with perioperative mortality risk but rather with the potential for benefit to the patient. And when you're dealing with the sickest patients, often they achieve the highest benefit even though the perioperative mortality risk may be a little higher. We all know that the healthiest patients are the ones who do best after any operation.

Dr. McLaughlin. We've had a very similar experience. In fact we reviewed this in some detail last year for a presentation at Dr. Jones' seminar at Duke.

And our patient ages are almost identical. They're about 63 or 64 years of age. The interesting part is that we're somewhat surprised to find that the quality of ventricle has not changed much. It's still mainly 60% to 70% reasonably good ventricle. We do see many more patients in unstable condition. We've had some increase in the female *versus* male population.

Interestingly, in this study, male and female patients had an identical outcome throughout the duration of the study from time of operation to survival follow-up. They had an identical survival curve, and that's actually been our experience for a long time.

I think the future is quite bright. The problems with the saphenous vein graft are amenable to scientific investigation and are amenable to solution. We've been focusing on the role of the endothelium. The recognition that the endothelium is a metabolically active structure that can be damaged or destroyed by vein-graft preparation is a very important concept.

It produces prostacyclin, endothelial-dependent relaxing factors, various heparinlike substances, a whole list of good things the endothelium will produce if it's intact. And we believe that these vein-graft atherosclerotic changes probably start in the perioperative period with damage to the veins.

As a result of our studies, we've changed from saline solution now to a balanced salt solution with 2.5 g of albumin per liter. And this has been demonstrated in our experiments to affect endothelial preservation. So I think the technical refinements will continue.

And I think the other great problem we need to solve in these older patients is the issue of stroke. In these 75-, 80-, and 85-year-old patientss we're experiencing a 5% to 10% risk of stroke, which I think really does temper one's enthusiasm for operation in patients who are reasonably stable. If this problem can be solved, I think that will help also.

But I think the future is bright. And I think we're going to see that until we find an actual cure for the disease of atherosclerosis, not just control of risk factors but the cause of the disease and then a cure. Mechanical reconstruction of the circulation with new conduits is going to remain the only way to deal with extensive coronary disease because of the high rate of recurrent problems with all of the other methods of recanalization.

As far as the Posch study is concerned, this is extremely interesting data. But the data in that study really relate to a group of people with hyperlipidemia. Based on our view of what is normal and what is abnormal, most of our patients really didn't have hyperlipidemia.

The surgically treated population in all our studies behaved quite differently from the patients who were treated medically in terms of survival. In a way the operation appears to neutralize the risk of disease progression. There is no doubt that progression of coronary disease can be diminished by very intensive lipid control in severely hyperlipidemic patients.

The controversy is—and this is, I think, a national controversy—what to do with the patient who is reasonably healthy with a cholesterol level of 220 to 240? Should these people be subjected to lipid lowering?

And there's absolutely no shred of data anywhere, including the Framium study, that demonstrates any benefit for lipid lowing or lower lipid levels in patients older than 50 years. And there never has been a report demonstrating reduction in mortality rate from lipid lowering in any of the randomized studies of lipid lowering by medication.

Although there may be apparent differences, I don't think the differences are very great because of the quite substantial differences in baseline populations.

Intraoperative Identification of Cardiac Patients at Risk to Develop Postoperative Atrial Fibrillation

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Postoperative atrial fibrillation (AF) is a complication occurring in 11% to 36% of patients after cardiac operations, which results in increased morbidity and hospital costs. A new electrophysiologic screening test was developed to identify those patients at risk for development of postoperative AF. The test was validated in 50 patients (43 men and 7 women) with a mean age of 59.6 ± 1.3 years who underwent coronary artery bypass grafting with or without other cardiac surgical procedures. After aortic and venous cannulation, but before initiation of bypass, the mid-right atrium was stimulated with a bipolar probe at 25 μA for 3 seconds. Alternating current was increased by 25 μA until AF was induced or up to a maximum of 200 μA. Postoperative AF occurred in 18 patients (36%), 17 of whom had inducible AF (sensitivity = 0.94). Of the remaining 32 AF-free patients, 13 had negative tests (specificity = 0.41). Age and sex were not factors affecting inducibility, although patients who developed AF were older than those who were AF free (63.6 *versus* 57.3 years, p = 0.02). Length of stay in the intensive care unit was longer for those with postoperative AF than for AF-free patients (3.6 *versus* 1.9 days, p = 0.02). The negative predictive value of the test was 0.93, and the positive value was 0.47. These data show that this new intraoperative technique may be used to identify patients at risk for postoperative AF. Prophylactic therapy can therefore be directed to only those patients at risk for postoperative AF.

ATRIAL FIBRILLATION (AF) IS a common dysrhythmia occurring in 11% to 36% of patients after cardiac surgical procedures.[1,2] This complication may add to the morbidity and mortality rates of surgery and often results in increased hospital stay and patient costs.

Many studies have assessed drug prophylaxis against the development of postoperative AF. Digoxin alone may decrease the incidence of AF[1,3,4] but increases the likelihood of ventricular dysrhythmias.[5,6] Beta blockade has been effective in controlling AF after surgery with infrequent side effects.[7-9] The use of calcium channel-blockers for control of AF is either frequently associated with significant side effects or is not successful in converting AF to sinus rhythm.[10,11] The major clinical problem with prophylactic treatment of AF is that 60% to 90% of postoperative cardiac patients would be given medication unnecessarily.

Rather than prophylactically treat all patients for AF, it would be preferable to develop an intraoperative electrophysiologic test that could identify patients at risk for development of postoperative AF. Appropriate prophylaxis could then be directed to this group, which would decrease cost and side effects of the therapy and also reduce the incidence of AF. The purpose of this study was to assess a new electrophysiologic screening technique to identify patients at risk for development of postoperative AF.

Materials and Methods

Fifty patients undergoing elective and urgent coronary artery bypass grafting with or without other cardiac procedures performed by one surgeon at Duke University Medical Center were consecutively enrolled in the study. Patient clinical characteristics and preoperative medications were recorded. Beta- and calcium channel-blocking drugs were continued until the morning before surgery but were withheld after operation unless required specifically for dysrhythmia treatment.

After anesthesia and median sternotomy, patients underwent single-stage venous and ascending aortic cannulation for cardiopulmonary bypass. Before the initiation of cardiopulmonary bypass, the mid-right atrial free wall

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was stimulated through a hand-held bipolar probe for 3 seconds using an alternating current of 25 μA. The current was increased by increments of 25 μA until AF was induced or until a maximum stimulating current of 200 μA was delivered. If AF was inducible, the test was considered to be positive, but if no AF developed using up to 200 μA, a negative result was recorded. After surgery, patients were taken to the intensive care unit (ICU), where their limb lead II electrocardiograms (ECGs) were continuously monitored. On transfer to a step-down unit, ECGs were monitored continuously by telemetry until discharge. Episodes of postoperative atrial fibrillation were considered to be significant only if they were sustained for more than 30 minutes or resulted in hemodynamic instability requiring treatment.

Statistical Analysis

Results were analyzed using SAS Statistical Software (SAS Institute, Carey, NC). Continuous variables were assessed using unpaired Student's t tests. Discrete variables were analyzed using chi square contingency tables or two-tailed Fisher's exact tests when cell numbers were less than 5. A probability value of less than 0.05 was considered to indicate statistical significance.

Results

A total of 50 patients undergoing cardiac surgery by the senior surgeon were consecutively enrolled into the study. The mean age of all patients was 59.6 ± 1.3 years (range, 35 to 78 years), with seven women and 43 men. All patients underwent coronary artery bypass grafting, but there were 12 patients who had additional procedures including: left ventricular (LV) aneurysmectomy ± endocardial resection (n = 9), aortic valve replacement (n = 1), and Wolff-Parkinson White syndrome (WPW) pathway ablation (n = 2). Except for three patients, all were receiving either β-blockers (n = 35) or calcium channel-blockers (n = 43) before surgery. There was no correlation between preoperative medication and inducibility of AF or incidence of postoperative AF. The mean ejection fraction was 43.3 ± 1.7%, with a range of 20% to 66%. Patients undergoing only coronary bypass had an average of 4.0 ± 0.04 grafts, with the cross-clamp being 31.5 ± 2.0 minutes. Total bypass time was 111.7 ± 6.2 minutes. The mean length of stay in the ICU for all patients was 2.5 ± 0.3 days, with an overall hospital stay of 10.2 ± 0.6 days.

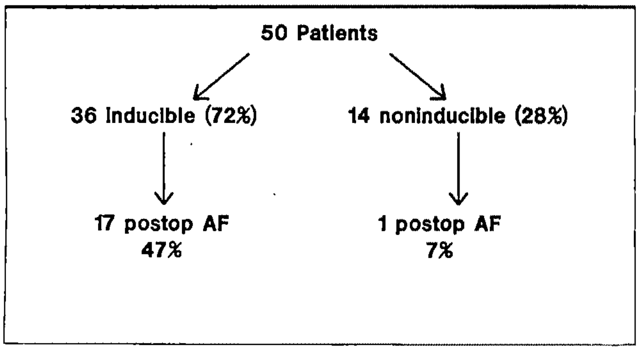

FIG. 1. Thirty-six patients had inducible sustained or nonsustained atrial fibrillation at the time of operation. Of these 36 inducible patients, 17 developed postoperative atrial fibrillation requiring therapy. Fourteen patients had noninducible intraoperative atrial fibrillation and only one developed postoperative atrial fibrillation. Therefore the positive predictive value of the test is 0.47 and the negative predictive value of the test is 0.93. If prophylactic therapy was directed only toward those who were inducible during operation, then only 38% of inducible patients would receive prophylactic therapy unnecessarily. However, if prophylactic therapy was given to all patients, then 64% would have received postoperative prophylactic therapy unnecessarily.

TABLE 1. *Patient Characteristics when Grouped According to Intraoperative Inducibility of Atrial Fibrillation*

	Noninducible	Inducible
N	14	36
Age (yrs)	56.6 ± 2.5	60.7 ± 1.5
Ejection fraction (%)	38.5 ± 2.3	45.0 ± 2.0
Cross-clamp time (mins)	32.9 ± 4.2	31.0 ± 2.2
Length of stay (days)	9.8 ± 0.7	10.4 ± 0.7
Postoperative AF	1	17

Mean ± SEM.
Postoperative AF, postoperative atrial fibrillation.

Using the screening test for AF, a total of 36 patients (72%) were inducible during operation. In the postoperative period, 18 patients developed AF (36%). The first episode of AF occurred on the 2.3 ± 0.6 postoperative day. All patients were treated with medications initially, with three requiring cardioversion before discharge. Of 32 patients who did not develop postoperative AF, 13 had a negative test (*i.e.*, specificity = 0.41). Of the 18 patients who developed postoperative AF, 17 had a positive test (*i.e.*, sensitivity = 0.94). The negative predictive value of the test was 0.93, and the positive predictive value was 0.47 (Fig. 1).

When comparing the patients according to inducibility of AF, there were no differences in age, ejection fraction, cross-clamp time, or length of stay in hospital (Table 1). In the patients who developed AF after operation, however, age was significantly greater compared with those without AF (63.6 *versus* 57.3 years, respectively; p = 0.02), and the length of stay in the ICU was longer (3.6 *versus* 1.9 days; p = 0.02). There was one death, in a 56-year-old man who required bypass grafting and LV aneurysmectomy who developed severe postoperative atrial and ventricular dysrhythmias.

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Discussion

The actual incidence of AF complicating the postoperative course after cardiac surgery varies in different series from 11% to 36%.[1,2,12-14] The wide range in frequency of AF may be explained by differences in how patients are monitored after operation, what constituted a reportable episode of AF and difficulty in distinguishing one supraventricular tachyarrhythmia from another. Valve surgery is more likely to result in postoperative atrial dysrhythmias than coronary artery bypass procedures.[12,15] In the present study, all patients underwent coronary artery bypass grafting ± other cardiac procedures, with 36% of patients developing postoperative AF.

Despite the large number of series assessing postoperative AF, no clear risk factors have been identified.[1] Older patients may be more susceptible to AF,[16-19] which was confirmed by the results of this study. Initially the withholding of β-blockers before operation was thought to contribute to a postoperative withdrawal syndrome, which included the development of atrial dysrhythmias. This concept has been disproven, however, when assessed in a prospective manner.[5,10,16,18,20] Some authors have suggested that the frequency of postoperative AF increases with longer aortic cross-clamp times,[17,18] whereas others can identify no such relationship.[21,22] Cross-clamp time was not a significant factor in the development of AF in the present study. Irritation of the atria during surgery may be a factor in increasing risk of AF,[6,21] as may be inadequate atrial preservation.[22-24]

Because AF is considered a preventable problem, numerous studies assessing prophylactic drug therapy have been performed. Digoxin has been shown to be useful in preventing postoperative AF,[1,3,4] although the incidence of ventricular dysrhythmias may be increased by digoxin.[5,6] Beta-blockers have been used widely with mixed success in controlling AF,[2,7-10,13,14,16,25,26] with a low incidence of side effects.[2,9,27] Calcium channel-blockers have been found to effectively control the ventricular response rate, but are less likely to result in conversion of the patient to sinus rhythm[11,28,29] and are associated with frequent side effects.[10]

Although postoperative AF rarely leads to catastrophic outcomes, it frequently leads to patient anxiety or discomfort and may result in longer hospital stays.[30] In the present study, the length of stay in the intensive care unit was significantly prolonged by an average of 1.7 days in patients with AF. In addition cerebrovascular accidents are more frequent in patients with postoperative AF.[31] For these reasons and the fact that high-risk patients cannot be identified by preoperative clinical characteristics, a new electrophysiologic test was designed to assess during operation the risk for postoperative AF.

The test is simple to perform and adds only 2 to 3 minutes to the operating room time. The results show that it has a high sensitivity, resulting in few missed patients who develop AF. It has a moderate specificity, which will lead to a significant number of false-positives. If prophylaxis was to be applied to just the patients with positive tests, however, then only 38% of patients would receive prophylaxis unnecessarily, compared with 64% if no screening test was used and all patients were treated.

In summary these data indicate that postoperative AF is a common complication of cardiac surgery that leads to increased time spent in the ICU. A simple, quick test to assess AF inducibility may be useful to identify patients in whom prophylactic treatment could be directed. The benefits may include a decrease in drug usage and resulting side effects, a shortened ICU stay, and decreased hospital costs, while qualitatively improving patient recovery.

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DISCUSSIONS

DR. FRED CRAWFORD (Mt. Pleasant, South Carolina): I would like to commend Dr. Lowe and his coauthors for this attempt to clarify a topic that has been discussed at some length over the years without definite conclusions being reached.

As the authors indicate, atrial fibrillation commonly occurs after cardiac surgical procedures. While it is a nuisance and without serious consequences in many patients, it can produce morbidity and, as the authors indicate, may prolong the stay in the intensive care unit and in the hospital.

Because of the frequent occurrence of this problem, many authors have tried to address it with either retrospective or prospective studies. In fact there are available in the literature both prospective and sometimes randomized studies to support virtually any position one would like to take insofar as the administration of various drugs before and after operation to prevent atrial fibrillation.

Certainly all of our patients would be well served if a simple test such as that described by the authors were available that would prospectively select out those at higher risk for the development of AF after operation so that they might be appropriately medicated, and at the same time allow the avoidance of medication for those at low risk.

The study by Lowe and colleagues attempts to do this. I have several questions of the authors.

First how did you decide on an upper limit of 200 microamps for your atrial stimulation?

Have you looked at your data to see if stimulation at a lower level would weed out many of the false positives, thus producing a higher predictive value?

If the tests were consistently successful in predicting a group at higher risk for atrial fibrillation, what would be your current drug of choice for prophylaxis against this development?

And, finally, have you applied the test prospectively and combined it with your drug of choice to see if the postoperative incidence of atrial fibrillation in your patients can be decreased?

DR. JOHN HAMMON (Nashville, Tennessee): I congratulate Dr. Lowe and his colleagues on a study that attempts to solve a very vexing problem for cardiac surgeons. That is the routine coronary patient who seems to be doing well, develops atrial fibrillation, and then develops a stroke or a low-cardiac-output peripheral embolism. This is truly a serious problem in our experience and the experience of others. I think Dr. Lowe's identification of these patients brings forward a new way of looking at this problem, which, in our experience is very valuable.

We performed a study several years ago in which we randomized a group of patients to receive propranolol after the operation immediately on arrival to the intensive care unit for the control of atrial and ventricular arrhythmias and found that this drug was very valuable in doing this. However in many of our patients who were older or sicker with bad ventricles, the propranolol dosage could not be adjusted to levels where prophylaxis could be induced. And therefore if we could identify a higher-risk group of patients, perhaps, better drug regimens could be recommended for this group of patients.

I have one question regarding the study. I think in our own experience in inducing ventricular fibrillation and measuring fibrillation and defibrillation thresholds in the operating room, we found that during the time of induction of anesthesia, during the time of cannulation for cardiopulmonary bypass, and immediately after cardiopulmonary bypass, these thresholds can be altered, perhaps by increased levels of plasma epinephrine, and norepinephrine, which have been measured in our laboratories. I was wondering if Dr. Lowe would comment on this feature.

Also I wonder if the large group of patients who were positive in his study might have been influenced by the rather heterogeneous group of patients he studied, rather than taking a group of patients purely with coronary disease.

DR. JAMES E. LOWE (Closing discussion): Dr. Crawford we chose 200 microamps in this initial protocol as the upper limit of stimulation because of the tremendous safety margin required with the use of alternating current. As you implied, patients who developed intraoperative atrial fibrillation at lower stimulating currents were indeed more likely to develop postoperative atrial fibrillation. In other words, those who went into AF in the operating room, either sustained or nonsustained, at 75 to 100 microamps had a 70% incidence of postoperative AF. However, if we did not include those patients who were stimulated up to 200 microamps, we would have missed a number of patients who developed postoperative AF and therefore had some false-negative intraoperative studies. The crux of the matter is that if you stimulate with too high a level of alternating current, you will increase the number of people who are placed in the at risk group. However if you don't stimulate with high enough amounts of alternating current, you will have a false sense of security in the negative group.

Obviously we will learn more in the future by applying this protocol to large numbers of patients. We do plan a prospective study that will allow us to direct prophylactic therapy after operation to all patients who had inducible AF during operation. We hope that we might be able to reduce the incidence of postoperative AF in our unit from 36% to 5% to 10%. We believe that applying prophylactic therapy to those patients at risk for atrial fibrillation will significantly reduce total hospital costs and eliminate the morbidity resulting from perioperative AF. As for the drug of choice, we are still undecided. We probably will use intravenous procainamide administered just before discontinuation of cardiopulmonary bypass with subsequent postoperative digitalization in those patients who have no ventricular arrhythmias.

Dr. Hammon suggested that there are variations at different points in time in AF thresholds. I believe that he is exactly right. The threshold may depend on circulating catecholamines and the amount of irritation to the atria at the time of cannulation.

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Can be supplemented with prn narcotic for severe or "breakthrough" pain

TORADOL IM and narcotics may be administered concomitantly but not in the same syringe.

References: 1. Brandon Bravo LJC, *et al*. The effects on ventilation of ketorolac in comparison with morphine. *Eur J Clin Pharmacol*. 1988;35:491-494. **2.** Camu F, *et al*. Hemodynamic effects of ketorolac tromethamine in comparison to morphine in anesthetised patients. In: 9th World Congress of Anaesthesiologists, Abstracts Volume I: Scientific Papers A0001 to A0506; May 22-28, 1988; USA. Abstract A0167. **3.** Data on file, Syntex Laboratories, Inc. (ICM studies: 994, 1060, 1254, 1302). [TORADOL 30 mg IM (N=509), morphine 10 mg/12 mg IM (N=151); TORADOL 30 mg IM (N=103), meperidine 100 mg IM (N=102). Nausea: TORADOL 8%, morphine 21%/TORADOL 3%, meperidine 20%; Vomiting: TORADOL 5%, morphine 9%/TORADOL 1%, meperidine 12%; Somnolence: TORADOL 14%, morphine 34%/TORADOL 6%, meperidine 14%; CNS Effects: TORADOL 23%, morphine 44%/TORADOL 21%, meperidine 30%.] **4.** Data on file, Syntex Laboratories, Inc. (ICM study: 1324).

* As with other nonsteroidal drugs, the most frequently reported side effects are gastrointestinal, with some GI symptoms reported by 3% to 9% of patients in clinical trials. See "Warnings," "Precautions" and "Adverse Reactions" sections of product information.

TORADOL® IM (ketorolac tromethamine) is a product of Syntex Laboratories, Inc.

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Please see summary of product information on following page.

P.I. 1289
17-90-8000-004-011

TORADOL® IM (ketorolac tromethamine)

Brief Summary

TORADOL is a nonsteroidal anti-inflammatory drug (NSAID). TORADOL 15 mg/mL solution contains 10% (w/v) alcohol, USP, and 6.68 mg sodium chloride in sterile water. The 30 mg/mL solution contains 10% (w/v) alcohol, USP, and 4.35 mg sodium chloride in sterile water. The pH is adjusted with sodium hydroxide or hydrochloric acid. **Indications and Usage:** Indicated for the short-term management of pain. Not recommended for use as an obstetrical preoperative medication or for obstetrical analgesia because it has not been adequately studied and because of the known effects of NSAIDs on uterine contraction and fetal circulation. Not recommended for routine use with other NSAIDs because of the potential for additive side effects. TORADOL protein-binding is affected by aspirin but not by acetaminophen, ibuprofen, naproxen or piroxicam. Studies with other NSAIDs have not been done. Has been used concomitantly with morphine and meperidine without adverse interactions. **Contraindications:** Do not use in patients with hypersensitivity to ketorolac or with the complete or partial syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other NSAIDs. **Warnings:** Although TORADOL Injection is recommended for short-term use only, long-term administration of oral ketorolac has shown that this drug shares the risks of other NSAIDs when taken chronically. Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Remain alert for ulceration and bleeding in such patients, even in the absence of previous GI tract symptoms. In clinical trials, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3–6 months, and in about 2–4% of patients treated for 1 year. Inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. Studies have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events, and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than others and most spontaneous reports of fatal GI events are in this population. High doses of an NSAID probably carry a greater risk of these reactions. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity. **Precautions:** Impaired Renal or Hepatic Function: As with other NSAIDs, use with caution in patients with impaired renal or hepatic function, or a history of kidney or liver disease. Renal Effects: As with other NSAIDs, long-term administration to animals resulted in renal papillary necrosis and other abnormal renal pathology. In humans, hematuria and proteinuria have occurred in long-term trials with oral ketorolac with a frequency and degree similar to aspirin. A second form of renal toxicity has been seen in patients with conditions leading to a reduction in blood volume and/or renal blood flow. In these patients, an NSAID may precipitate overt renal failure. Patients at greatest risk are those with impaired renal function, heart failure, liver dysfunction, taking diuretics, and the elderly. Discontinuation of the NSAID is typically followed by recovery. Use with caution in patients with impaired renal function as reduced creatinine clearance results in reduced clearance of the drug. Follow such patients closely. Fluid Retention and Edema: These have been reported with NSAIDs; use TORADOL with caution in patients with cardiac decompensation, hypertension, or similar conditions. Hepatic Effects: With NSAIDs, borderline elevations of liver tests may occur in up to 15% of patients. These may progress, remain unchanged, or disappear with continued therapy. Elevations of ALT (SGPT) or AST (SGOT) occurred in clinical trials with oral ketorolac in less than 1% of patients. Evaluate a patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, for evidence of a more severe hepatic reaction. Hematologic Effects: TORADOL inhibits platelet aggregation and may prolong bleeding time but does not affect platelet count, prothrombin time (PT) or partial thromboplastin time (PTT). Carefully observe patients with coagulation disorders or who are receiving drug therapy that interferes with hemostasis. Inhibition of platelet function by TORADOL disappears within 24–48 hours after the drug is discontinued. In clinical studies, the incidence of clinically significant postoperative bleeding was 0.4% compared to 0.2% in the groups receiving opiates. *Drug Interactions:* TORADOL is highly bound to plasma protein (mean 99.2%), independent of concentration. *In vitro* binding of warfarin to plasma proteins is slightly reduced by TORADOL (99.5% control vs 99.3% with TORADOL 5–10 μg/mL). TORADOL does not alter digoxin protein binding. At therapeutic concentrations of salicylate (300 μg/mL), *in vitro* binding of TORADOL was reduced from 99.2% to 97.5%, a potential 2-fold increase in unbound TORADOL plasma levels; hence, use TORADOL with caution (or at a reduced dosage) in patients being treated with high dose salicylate regimens. Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, acetaminophen, phenytoin, tolbutamide and piroxicam did not alter TORADOL protein binding. In a study of 12 healthy volunteers given TORADOL 10 mg orally for 6 days prior to co-administration of a single dose of warfarin 25 mg, no significant changes in pharmacokinetics or pharmacodynamics of warfarin were detected. In another study of 12 healthy volunteers, co-administration of heparin 5000 U s.c. and TORADOL did not show any pharmacodynamic effects of the combination on template bleeding time or kaolin cephalin clotting time. There is no evidence that TORADOL induces or inhibits the hepatic enzymes capable of metabolizing itself or other drugs. Some NSAIDs inhibit renal lithium clearance, leading to increased plasma concentration. This has not been studied with TORADOL. Some NSAIDs reduce the clearance of methotrexate, enhancing its toxicity. This has not been studied with TORADOL. TORADOL has been administered concurrently with morphine in clinical trials without adverse interactions. *Carcinogenesis, Mutagenesis, and Impairment of Fertility:* Studies in mice and rats at oral doses equal to or 2.5 times the parenteral MRHD (Maximum Recommended Human Dose), respectively, showed no evidence of tumorigenicity. Ketorolac was not mutagenic in tests with S. typhimurium, S. cerevisiae, or E. coli and did not cause chromosome breakage in the *in vivo* mouse micronucleus assay. Impairment of fertility did not occur in male or female rats at oral doses 4.5 and 8 times the parenteral MRHD, respectively. *Pregnancy:* Pregnancy Category B: Reproduction studies in rabbits and rats with daily oral doses 1.8 and 5 times the parenteral MRHD, respectively, did not reveal evidence of harm to the fetus. Ketorolac caused delayed parturition and dystocia in rats at oral doses higher than the parenteral MRHD, like other NSAIDs. There are no adequate and well-controlled studies in pregnant women. TORADOL should be used during pregnancy only if clearly needed and no known safer alternatives are available. *Labor and Delivery:* TORADOL is not recommended for use during labor and delivery. *Lactation and Nursing:* After a single oral dose of TORADOL 10 mg to humans, the maximum milk concentration was 7.3 ng/mL and the maximum milk-to-plasma ratio was 0.037. After one day of dosing (qid), the corresponding values were 7.9 ng/mL and 0.025. Use caution when TORADOL is administered to a nursing woman. *Pediatric Use:* TORADOL is not recommended for use in children. *Use in the Elderly:* Because ketorolac is cleared more slowly by the elderly, who are also more sensitive to renal effects of NSAIDs, use extra caution and reduced dosages when treating the elderly. **Adverse Reactions:** Adverse reaction rates from short-term use of NSAIDs are generally 1/2 to 1/10 the rates associated with chronic usage. This is also true for TORADOL. In studies of patients treated for up to 1 year, the incidence of serious and nonserious ADRs, including GI tract ulceration and bleeding (yearly rate 1.2 to 5.4%), associated with oral ketorolac 10 mg, 1 to 4 times per day prn, was comparable to treatment with aspirin 650 mg prn. Be alert for the usual complications of NSAID treatment. The adverse reactions listed below were reported to be probably related to TORADOL in trials in which patients received up to 20 doses of TORADOL 30 mg IM in 5 days. *Incidence greater than 1%:* Body as a whole: edema. GI: nausea,* dyspepsia,* GI pain,* diarrhea. Nervous system: drowsiness,* dizziness, headache, sweating. Injection site pain was reported by 2% of patients in multidose studies (vs 5% for morphine). *Incidence of reported reaction 3%–9%. Reactions occurring in less than 3% are unmarked. *Incidence 1% or less:* Body as a whole: asthenia, myalgia. Cardiovascular: vasodilation, pallor. Dermatologic: pruritus, urticaria. GI: constipation, flatulence, GI fullness, liver function abnormalities, melena, peptic ulcer, rectal bleeding, stomatitis, vomiting. Hemic and lymphatic: purpura. Nervous system: dry mouth, nervousness, paresthesia, abnormal thinking, depression, euphoria, excessive thirst, inability to concentrate, insomnia, stimulation, vertigo. Respiratory: dyspnea, asthma. Special senses: abnormal taste, abnormal vision. Urogenital: increased urinary frequency, oliguria. **Drug Abuse and Physical Dependence:** TORADOL is not a narcotic agonist or antagonist. Subjects did not show any symptoms or signs of withdrawal upon abrupt discontinuation of IV or IM dosing. Patients receiving TORADOL orally for ≥ 6 months have not developed tolerance and there is no pharmacologic basis to expect addiction. TORADOL did not exhibit activity in classical animal studies which are reasonable predictors of opiate analgesic action. *In vitro,* TORADOL does not bind to opiate receptors. Thus, TORADOL does not have central opiate-like activity. **Overdosage:** Lack of experience with acute overdosage precludes characterization of sequelae and assessment of antidotal efficacy. At single oral doses > 100 mg/kg in rats, mice and monkeys, symptoms such as decreased activity, diarrhea, pallor, labored breathing, rales, and vomiting were observed. **Dosage and Administration:** TORADOL may be used on a regular schedule or prn, although current recommendations for pain management are to use analgesics on a regular schedule rather than prn based on the return of pain. For the short-term management of pain the recommended initial dose is 30 or 60 mg IM as a loading dose, followed by half of that (15 or 30 mg) every 6 hours as long as needed to control pain. The recommended maximum total daily dose is 150 mg for the first day and 120 mg/day thereafter. The lower end of the dosage range is recommended for patients under 50 kg (110 pounds), for patients over 65 years of age, and for patients with reduced renal function. CAUTION: Federal law prohibits dispensing without prescription.

TORADOL® IM (ketorolac tromethamine)

U.S. Patent No. 4,089,969 and others.

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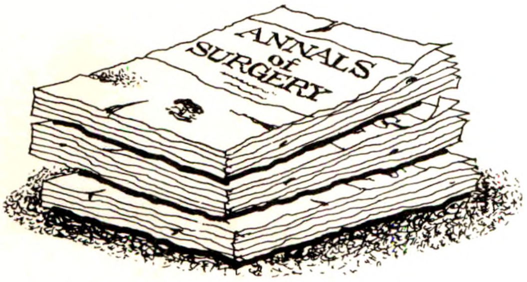

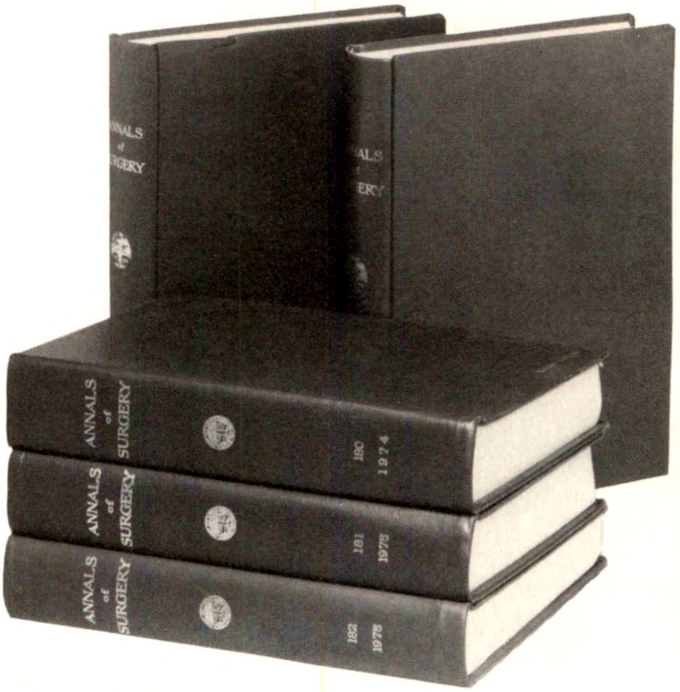

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Heart Transplantation in Children

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Orthotopic cardiac transplantation has been performed in 15 consecutive neonates and children since 1987. Diagnoses include hypoplastic left heart syndrome (5 patients), critical aortic stenosis with small left ventricle (1 patient), complex cyanotic heart disease (6 patients), and cardiomyopathy (3 patients). Twelve patients survived operation and have been followed from 1 to 45 months. Patients less than 6 years of age are managed with cyclosporine ± azathioprine; in older patients steroid weaning is attempted. Monitoring for rejection is performed with serial echocardiography in patients under 6 years of age; older patients undergo serial biopsies. Actuarial freedom from rejection was 26% 3 months after operation; 47% were free of infection 6 months after operation. There have been no late deaths. Actuarial survival at 3 years is 79%. Nine patients have undergone postoperative catheterization. Resting hemodynamics were normal in every patient. All long-term survivors are asymptomatic and fully active. It is concluded that cardiac transplantation in neonates and children is an effective treatment option for end-stage cardiomyopathy or otherwise incurable congenital heart disease. Long-term survivors have excellent potential for full rehabilitation.

CARDIAC TRANSPLANTATION HAS gradually evolved from consideration as an experimental procedure in 1968 to a well-established therapeutic modality in 1990. It has become an accepted form of treatment for adults with end-stage cardiomyopathy with no alternative standard medical or surgical treatment options. In recent years the addition of cyclosporine to the immunosuppressive regimen has lead to a decrease in the number of episodes of rejection and infection, and this drug has improved both the length and quality of life of adult patients after transplantation.[1]

Cardiac transplantation in infants was introduced in December 1967, when Kantrowitz[2] performed a heart transplant in a 3-week-old infant with tricuspid atresia. Very few transplants were performed in children throughout the 1970s. At Stanford University transplantation in children was initiated in December 1980. The use of cyclosporine, as well as improved recipient selection, has improved the survival rate of children undergoing cardiac transplantation such that the long-term results are comparable to those found in adults.[3]

In 1985 neonatal transplantation was introduced by Dr. Leonard Bailey[4] at Loma Linda University Medical Center as a treatment option for infants with the uniformly lethal hypoplastic left heart syndrome.

Cardiac transplantation in neonates and children differs significantly from cardiac transplantation in adults. Unique considerations include the complex congenital anatomic abnormalities of the recipient and the requirement that steroids be minimized to prevent growth arrest. Furthermore monitoring rejection with serial endomyocardial biopsies is more difficult and more dangerous in small children.

This report summarizes our experience with orthotopic cardiac transplantation in 15 consecutive infants and children at Vanderbilt University Medical Center.

Materials and Methods

From February 1987 through October 1990, 15 consecutive infants and children underwent orthotopic cardiac transplantation. All patients except one were 16 years of age or less and had complex congenital heart disease or cardiomyopathy. The diagnoses were hypoplastic left heart syndrome (5 patients), critical aortic stenosis with a small left ventricle (1 patient), complex cyanotic heart

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disease (5 patients), and idiopathic cardiomyopathy (3 patients). One additional patient 20 years of age had congenitally corrected transposition of the great arteries. Each patient with cyanotic heart disease had undergone at least one previous operation (Table 1).

Neonates with hypoplastic left heart syndrome were managed with continuous low-dose prostaglandin E_1 infusion to maintain ductal patency and systemic perfusion. As indicated neonates were also maintained in a low-oxygen environment (fraction of inspired oxygen [F_{IO_2}] < 0.21) to balance the systemic and pulmonary vascular resistances and to prevent florid pulmonary edema from excessive pulmonary blood flow. Other patients were managed with mechanical ventilation and inotropic support before operation as necessary. The mean time on the waiting list before operation was 29 ± 28 days (standard deviation [SD]) (range, 2 to 94 days). At the time of operation, 11 patients were United Network for Organ Sharing (UNOS) status 1 and four were UNOS status 2.

All patients underwent orthotopic cardiac transplantation. In the five patients with hypoplastic left heart syndrome, deep hypothermia and circulatory arrest technique was used. All other patients underwent transplantation using moderate hypothermia and cardiopulmonary bypass. Recipients and donors were matched with respect to body weight and ABO blood group compatibility. Donor cardiac protection was performed with a single dose of crystalloid cardioplegia and immersion of the donor heart in ice-cold Ringer's lactate. Cardiac protection at the time of implantation was aided by both topical and intracavitary cooling during the performance of the various anastomoses. The graft ischemia time was a mean of 203 ± 53 minutes (range, 79 to 263 minutes).

Before operation patients were given cyclosporine (5 to 10 mg/kg), depending on renal and hepatic function. Azathioprine (2 mg/kg) also was administered intravenously. At the time of aortic cross-clamp release, methylprednisolone (7.5 mg/kg) was administered. After operation three doses of methylprednisolone (3.5 mg/kg) were administered every 8 hours. After operation cyclosporine was administered, beginning at approximately 10 mg/kg/day. Whole-blood cyclosporine levels, as determined by high-pressure liquid chromatography, were maintained at approximately 200 ng/mL for the first 6 months. Neonates and children received azathioprine 1 to 2 mg/kg/day to maintain a white blood cell count of approximately 5000/mm^3. No prednisone was administered to the neonates routinely. The older children received prednisone (0.8 mg/kg/day), which was tapered to 0.2 mg/kg/day by 6 weeks after operation and was eventually discontinued in all patients less than 6 years old.

TABLE 1. *Previous Operations in Patients with Cyanotic Conditions*

Diagnosis	Previous Operation
TGA, IVC obstruction	Mustard
TGA, VSD, SVC obstruction	Mustard, VSD
Corrected TGA	VSD
Single ventricle, LSVC	Coarc, Band, B/T, B-Hanlon, A-P Window
Single ventricle, malposed	B/T, Mod B/T, B-Hanlon
Pulm atresia, IVS	B/T, Mod B/T (2), Central, B-Hanlon

TGA, transposition of the great arteries; IVC, inferior vena cava; VSD, ventricular septal defect; SVC, superior vena cava; LSVC, left superior vena cava; IVS, intact ventricular septum; Coarc, coarctation; B/T, Blalock-Taussig shunt; B-Hanlon, Blalock-Hanlon; A-P, aortopulmonary; Mod, modified.

In children older than 6 years of age, the diagnosis of allograft rejection was made by serial cardiac biopsy. The hallmark of rejection requiring treatment was myocyte necrosis. Neonates and children younger than 6 years were followed for rejection by clinical criteria and serial echocardiography only, a system developed jointly with Loma Linda University Medical Center. The echo indices indicative of rejection in neonates included detailed analysis of left ventricular wall mass and volume.

Hospitalized patients with allograft rejection were treated with intravenous methylprednisolone (250 mg twice a day or 15 mg/kg/day) for 3 days. Repeat biopsies or echocardiograms were performed 48 to 72 hours after completion of therapy to determine response to treatment. A second course of methylprednisolone was given if rejection was ongoing or if an independent second episode of rejection occurred. If a third episode of rejection occurred, rabbit antithymocyte serum was administered intravenously for 7 days at a dose of 0.2 mL/kg/day, and circulating T cells were monitored with the dosage adjusted to keep the total T cells less than 10%.[5] Two teenagers had persistent or recurrent rejection episodes and received a course of methotrexate, and one received a course of vincristine.

Outpatients who had documented rejection episodes were treated with an increase in the oral prednisone dose, which was then tapered over approximately 1 week. Follow-up evaluation with repeat biopsy or echocardiography was obtained to determine the response to treatment.

Actuarial curves were computed by the method of Kaplan-Meier and compared by the method of Gehan.[6,7] Linearized rates, expressed as events/100 patient-days, and calculated on a cumulative basis, were compared using the maximum-likelihood test ratio.[8]

Results

Fifteen consecutive patients have undergone orthotopic cardiac transplantation. Two of the five patients with hypoplastic left heart syndrome died in the operating room. One child had a severely hypoplastic right pulmonary artery and minuscule anomalous pulmonary veins detected only at the time of cardiectomy. This patient died of donor right ventricular failure. Another patient died of left ventricular failure caused by technical problems with the aortic anastomosis that resulted in residual aortic narrowing. One of the six patients with complex cyanotic heart disease died 1 week after operation of right ventricular failure thought to be due to persistently elevated pulmonary vascular resistance. The hospital stay after operation was 29 ± 22 days (range, 13 to 89 days).

There have been no late deaths. Actuarial survival at 36 months is 79 ± 11% standard error of the mean and is the same as in our adult heart transplant recipients (Fig. 1). Follow-up ranges from 1 to 45 months and is complete and timely in all patients.

The linearized rejection rate (events per 100 patient-days) was 1.4 and 0.67 at 1 and 3 months after operation, respectively. When compared with the adult patients, the linearized rejection rates were similar (Fig. 2). Actuarially at 1 month after operation, 62% of children were free from rejection, and only 26% were free from rejection 3 months after operation. A similar trend was noted in the adult patients (Fig. 3).

Infectious complications were due to bacterial, viral, and protozoan causes. There were no instances of fungal infection noted. A total of 20 episodes of infection occurred. These included four pulmonary infections, four urinary tract infections, three blood-borne infections, one episode of central line infection, one episode of mediastinitis, and seven other episodes. All patients recovered from their infections without significant residual problems.

An actuarial analysis of the percentage free from infection indicates that 85% of children were free of infection at 1 month after operation, and 47% were free of infection 6 months after operation. The actuarial curves for freedom from infection are similar for children and adults (Fig. 4).

Serum creatinine, blood urea nitrogen (BUN), and creatinine clearances were determined serially. In most neonates and children, these values were stable during the course of follow-up with minimal evidence of declining renal function. At the most recent follow-up, the mean BUN was 19.8 ± 6.7 mg/dL, the mean creatinine was 1.0 ± 0.38 mg/dL, and the mean creatinine clearance was 81 ± 48 mL/min/m^2.

Hypertension significant enough to warrant treatment was noted at most recent follow-up in 6 of the 12 long-term survivors. All of the children with hypertension are greater than 6 years of age and are still receiving corticosteroids as part of their immunosuppressive regimen. These patients were treated with either calcium channel-blockers or acetylcholinesterase inhibitors or both. In all instances excellent blood pressure control was obtained.

Three patients have each undergone three yearly follow-up cardiac catheterizations, one patient has undergone restudy at both 1 and 2 years after operation, and five additional patients have undergone follow-up study 1 year after operation. In all patients graft function is normal at rest. Only minor gradients have been detected across ar-

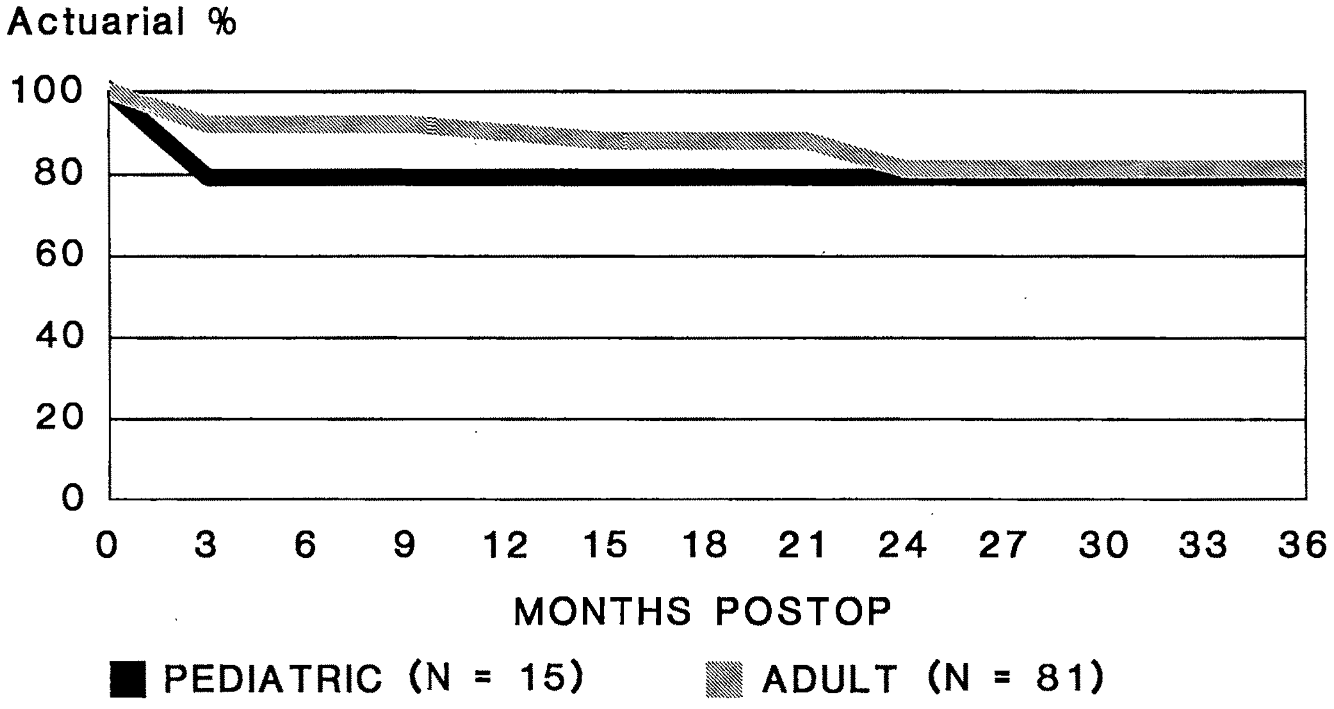

FIG. 1. Actuarial survival for pediatric and adult heart transplant recipients.

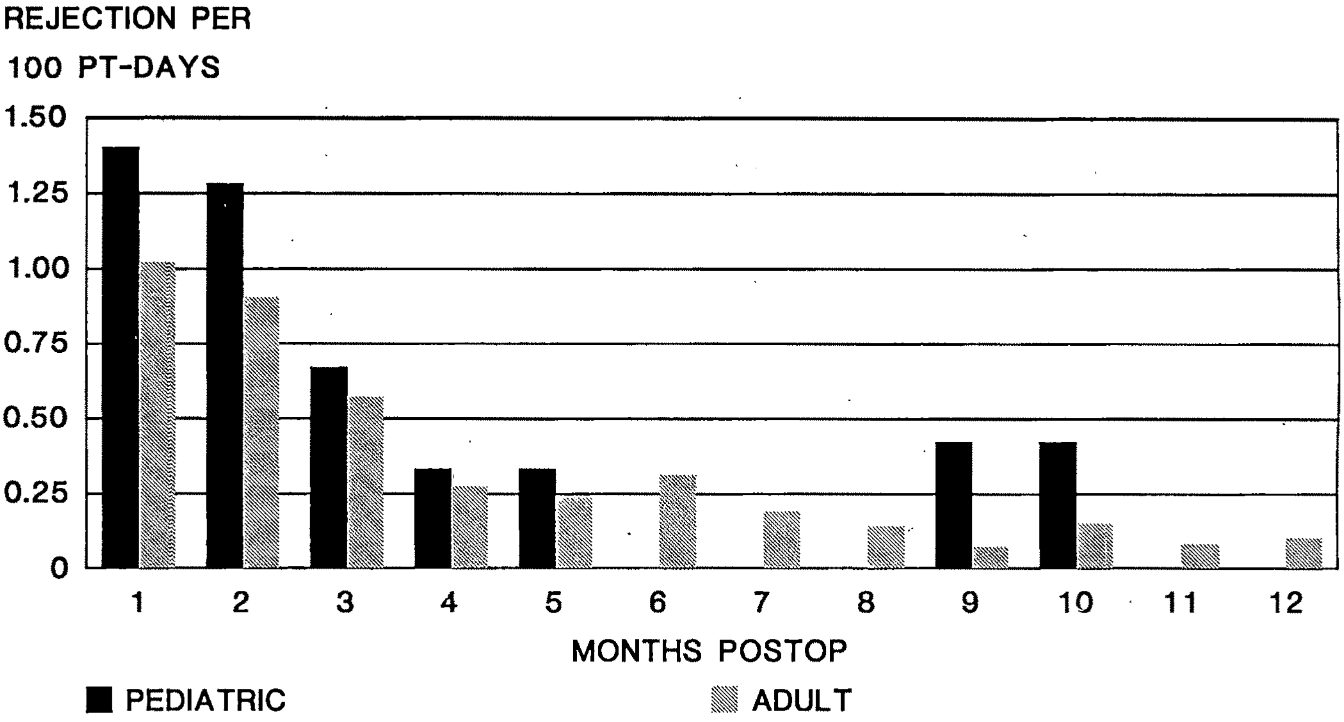

FIG. 2. Cumulative linearized rejection rate.

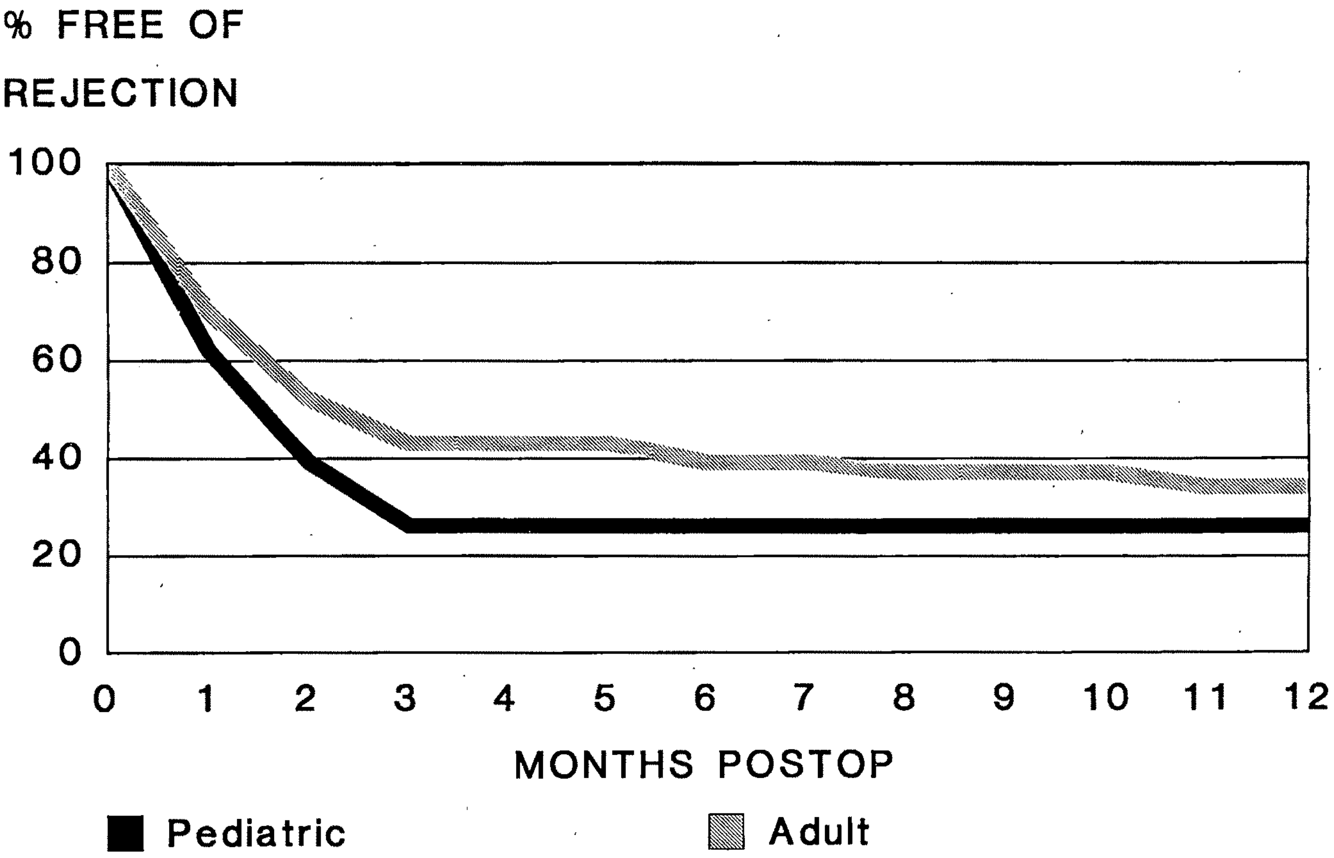

FIG. 3. Actuarial freedom from rejection.

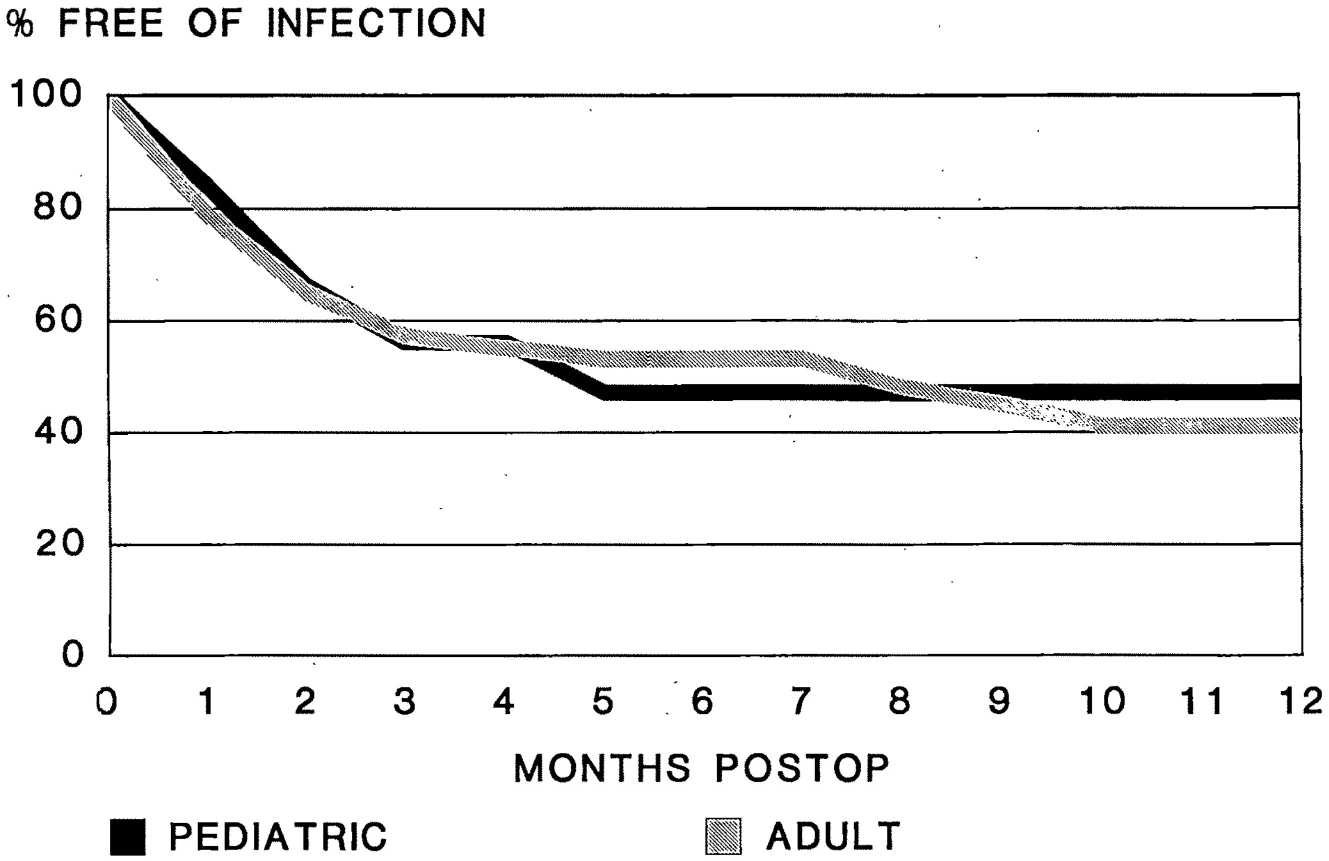

FIG. 4. Actuarial freedom from infection.

terial anastomoses, and no coronary artery disease has been noted.

All of the 12 long-term survivors are doing well and have no significant residual problems. No patient has symptoms related to cardiac transplantation. All are fully active and carrying out normal activities for their age.

Discussion

Heart transplantation in neonates and children has evolved into an accepted therapeutic modality for complex congenital heart disease and for end-stage cardiomyopathy when there are no medical or surgical treatment alternatives. Transplantation in young patients has gained acceptance due to improved immunosuppression and due to results that are comparable to those found in the adult experience. Pennington et al. have noted the rapid rise in the number of children undergoing heart transplantation.[9]

One of the major concerns in young children with heart transplants is the possibility of growth retardation.[10] Steroids have been implicated in retardation of skeletal growth.[11] Because of this potential problem, efforts have been extended to wean patients off steroids or to switch to an alternate-day steroid regimen in an attempt to minimize growth retardation.[12] It has been postulated that the newborn child may be the best possible recipient of organ transplantation because host immune responses are less aggressive and more easily controlled when transplantation is accomplished shortly after birth. It may be possible to sustain children who underwent heart transplantation as neonates with minimal immunosuppression, including the absence of steroids.[13]

Special problems are posed by the small size of neonates and young children with regard to the diagnosis of cardiac rejection. It is not feasible to perform frequent biopsies in infants and small children because of their small size and the need for anesthesia.[14] Nonetheless these young patients require frequent monitoring of rejection. In our experience the rate of rejection in children is similar to that in adults. Rejection is most frequent in the first several months after transplantation, but the need for monitoring rejection remains constant.

None of the neonates who have been followed for rejection by noninvasive echocardiographic criteria have died from untreated rejection. In this experience there has not been a higher frequency of treatment for rejection than in other series of children and adults followed by serial endomyocardial biopsy. The use of a multifactorial computer-assisted analysis of left ventricular volume, mass, contraction, and relaxation parameters has been largely responsible for the success of this noninvasive approach to the diagnosis of rejection.

Linear growth was achieved in all eight surviving neonates and children less than 6 years of age by the exclusion of prednisone from their immunosuppressive regimens. These patients have been treated with cyclosporine and azathioprine. In patients transplanted as neonates, azathioprine is discontinued after the first year. Thus far it seems that satisfactory and effective immunosuppression can be achieved in neonates and younger children without prednisone.

Orthotopic cardiac transplantation is technically feasible in neonates and small children even in the face of complex congenital cardiac abnormalities. In many patients with complex lesions and with functioning systemic to pulmonary artery shunts, accurate assessment of pulmonary vascular anatomy and resistance may be difficult. Distortion of pulmonary anatomy and elevation of pulmonary vascular resistance remain significant risk factors after operation.[15]

Thus far in our experience graft function has been followed only up to 3 years with consecutive annual cardiac catheterization. In all patients graft function at rest has remained normal. There has been no evidence of significant stenosis across the arterial anastomoses. Graft atherosclerosis has not been encountered.

In conclusion orthotopic cardiac transplantation in neonates and children is an effective treatment option for end-stage heart disease or otherwise incurable congenital heart disease. In properly selected patients, the perioperative mortality is low. There is excellent potential for full rehabilitation in the long-term survivors. Thus far these data, plus those presented by others, seem to indicate that cardiac transplantation in children should continue to be approached with cautious optimism.

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DISCUSSIONS

DR. TIMOTHY GARDNER (Glyndon, Maryland): One of the most exciting developments in the field of heart transplantation has been the realization that this therapy can be applied to children. These excellent data from Vanderbilt and clinical results from other transplant centers are making this point clear. It's also very gratifying to realize that patients with the otherwise untreatable or poorly treated entity of hypoplastic left heart syndrome may also be a target group for this therapy.

The experience at Johns Hopkins in the last several years parallels the results just presented by Dr. Merrill, with a couple of minor exceptions. Of our 14 patients who have had heart transplants—and there were several others that had heart-lung transplantation—nine of the patients had cardiomyopathies. The favorable experience in these patients who tend to be a bit older is not very surprising. There were many teenagers early on with cardiomyopathies, in the Stanford series and although they do present somewhat different considerations in the long term, this isn't the subgroup of young patients that creates the excitement.

It is the younger children, the infants, especially those who have hypoplastic left heart syndrome as well as those who have otherwise uncorrectable congenital defects for whom heart transplantation is so unique. Our experience at JHH has been exclusively with children having hypoplastic left heart syndrome.

We have not yet undertaken transplantation, at least heart transplantation, to treat children with complex and otherwise incurable congenital heart defects. Our survival data is very similar to that presented by Dr. Merrill. We have a 79% late survival rate, with two deaths in the cardiomyopathy group, while one of the five patients with the hypoplastic left heart syndrome have died.

Three of our five hypoplastic left heart syndrome patients had undergone stage 1 Norwood repair, had developed ventricular failure and were accepted for transplantation at that point.

We had two early deaths. Both of these two patients were moribund at the time of surgery. One late death occurred in an older child with cardiomyopathy who had persistent severe rejection, and had early changes of coronary artery disease in the grafted heart.

Our long-term management also includes cyclosporine and imuran. We attempt to taper or wean steroids, decreasing the dose during the first year. We have attempted frequent follow-up surveillance, but of these patients are not from our immediate geographic area and require follow-up by their pediatricians, which has generally been successful. As opposed to the Nashville group and to the experience at Loma Linda, we have tried to perform regular late biopsies to assess rejection, even in the younger children. This point leads to my first question to Dr. Merrill.

I'm especially interested in your initial or preliminary experience with the young children who do not haved regular biopsies. And I wonder if there may be a role for a prospective study of this approach.

Even though logistically it's difficult to put these young children through the same myocardial biopsy schedules, wouldn't it be better to study this group early on to ensure that one is not missing serious rejection or, alternatively, not overtreating these children especially with high-dose steroids?

My second question regards the management of neonates with hypoplastic left heart syndrome. What are inclusion criteria for transplantation of these infants? Who do you consider suitable for heart transplantation? Is there still a role for so-called compassionate care to these children? Many people question whether they should be treated at all. Are you attempting any staged Norwood repairs, and how do you decide among the various therapeutic options?

This is an exciting presentation, and we look forward to more follow-up from your group and from others doing this surgery.

Dr. Willis Williams (Atlanta, Georgia): I rise to compliment the Vanderbilt group not as a pediatric heart transplant surgeon but rather as an admiring and very grateful pediatric cardiac surgeon and a referring physician.

Could I have the slide? This now-famous photograph of Dr. Leonard Bailey from the Loma Linda Medical Center with several of his grateful patients stimulated interest in orthotopic cardiac transplantation as an alternative of care for the hypoplastic left heart syndrome.

It can't help but amaze us all that every infant in this photograph has an orthotopic heart transplant and all but one or two were placed for the hypoplastic left heart syndrome, a disease that has plagued pediatric cardiologists and has in many cases been treated by so-called compassionate care, simply lack of care, because the prognosis was so poor.

Three years ago we were fortunate to have Dr. Kirk Kanter join us on the Emory faculty with a special interest in transplantation. He was appointed the director of the transplantation service and had a special interest in congenital heart disease. He came just in time for me because a number of my patients managed over the years had really reached virtually the end of the road.

I had operated on this young man on the right nine times, beginning as an infant with pulmonary artery banding and then multiple attempts to repair a complicated defect, progressing finally through a series of pacemakers and pacemaker revisions after multiple attempts to repair the intracardiac anatomy.

This young man really had reached a state of profound depression, was absolutely moribund, and had lost his will to live. Following orthotopic cardiac transplantation, the remarkable change simply impressed me to a point that I have not yet been able to believe the remarkable recovery that can be made in children who I would otherwise have judged inoperable for any procedure.

Six months after the heart transplant, I saw this young man, my former patient, running up the street in front of the hospital in a sweat suit; he was jogging around the hospital. He had come back for one of his check-ups and was simply doing his physical workout for that day.

Now this young girl on the right with her sister had a Fontan operation after three previous systemic arterial-to-pulmonary-arterial shunts. The Fontan operation would have to be judged a failure by any criteria; she was in profound right heart failure with an enormous liver and ascites and peripheral edema. After orthotopic cardiac transplantation, she made a dramatic and rapid recovery and is asymptomatic.

When dealing with these small numbers, I believe that smiles and the condition of life for these children tell a great deal more than Kaplan-Meier survival curves or a Cox regression analysis.

I'm struck by the similarity of the numbers at the various institutions. Dr. Kanter and his colleagues at Emory have performed 13 cardiac transplantations in infants and children, with one in-hospital death and one late, sudden, unexplained death several months after the transplantation.

The other 11 children remain alive and well on minimal immunosuppressive therapy and with data that parallels very closely that described by Dr. Merrill and also by the experience at The Johns Hopkins Hospital.

This final slide illustrates the range for which this wonderful operation appears to have potential. On the right is the oldest of the Emory transplant recipients, a prominent Atlanta businessman, who continues to be one of the most avid supporters of the American Heart Association and an important fund-raiser in our community.

Being held by the mother is our youngest transplant recipient, an infant with the hypoplastic left heart syndrome for whom this operation remains life saving.

My questions for Dr. Merrill are simple.

First, Dr. Merrill, I would like to know, as indicated by Dr. Gardner, your philosophy of management for the hypoplastic left heart syndrome. Our management at Emory includes the offering to all parents of either the possibility of a heart transplant or, if no donor becomes available within 2 weeks, the initiation of the first-stage Norwood operation.

Unfortunately relatively few donors becomes available and, therefore, more of our patients with the hypoplastic left heart syndrome are still treated by the Norwood principles.

My final question relates to your selection of patients for 'bail-out,' as I would refer to it. How do you select the patients in whom other complex management procedures for congenital heart disease have failed.

The problem that we have confronted on many occasions is that of elevated pulmonary vascular resistance and the ability to distinguish it from elevated pulmonary venous pressure, left atrial pressure, and left ventricular failure, which, of course, would benefit from the transplantation of a new heart, in contrast to those children with pulmonary vascular obstructive disease, who would require heart-lung transplantation.

Do you have a protocol for the distinction of these two very important groups?

Dr. Ronald Busuttil (Los Angeles, California): I'm a bit puzzled by your observation of long-term, good renal function. As you know, the Stanford group, in a predominately adult population, has shown a deterioration of renal function over time.

In our own experience in liver transplantation, we've recently reviewed our first 100 pediatric liver cases and found that only 15% of the patients—if you measured true GFR—had a normal GFR.

I wonder, first, what are you doing to maintain your cyclosporine levels and what levels are you trying to achieve?

And, second, are you using any other agents to perhaps combat the nephrotoxicity that is clearly a penalty that we pay with cyclosporine?

We currently have a trial of using prostaglandins as an adjunctive measure to cyclosporine to see if we can decrease this.

Dr. Walter H. Merrill (Closing discussion): First, with regards to what Dr. Gardner had to say, he did make a comment about the problems of teenagers. And I think this is something that was not addressed in the presentation. But it's certainly a difficult age group to work with.

Our experience and that of many others is that teenagers, after a while when they're doing fine, have a tendency to stop coming to the doctor, to stop taking their medicines, and to engage in various practices that we would consider unhealthy for a heart transplant recipient. A great challenge awaits us in trying to discover how we might better take care of these teenagers and try to convince them to continue very scrupulous follow-up in medical care.

With regard to the assessment of rejection, I did not go into this in the presentation. But we do follow the younger children purely with echocardiographic assessment on a repeated basis. As Dr. Gardner alluded, there are certainly technical and other difficulties associated with the performance of multiple biopsies in these small children.

Thus far we've been very gratified with a scoring system developed jointly between our pediatric cardiologists and those at Loma Linda University Medical Center. I would only say that the incidence of rejection in these young people, as we have determined it by echocardiography, has been essentially the same as the incidence of rejection in these young patients detected in other centers by repeated biopsies.

And we can also say that no patient has died of rejection. So I think we have at least some success in the repeated evaluation of the presence or absence of rejection using echocardiography alone.

With regards to the care of patients with hypoplastic left heart syndrome and their selection for operation, it has been our policy in recent years to offer the option of heart transplantation to all children with hypoplastic left heart syndrome who did not have definite contraindications to the operation.

We have used the option, or at least considered the option, of performance of a Norwood procedure if the child had significant deterioration and a donor was not available. But to this point, at least, we've been very fortunate in that no children have died waiting for an organ.

With regard to the comments by Dr. Williams, I would echo his comments about the remarkable recovery potential of these young patients. Many of the children we've operated on have been critically ill, requiring intubation, multiple inotropic agents, and have really been virtually moribund. And to see a child go from this state subsequently to participating in normal activities is really very gratifying.

With regard to the selection of these patients with complex congenital heart defects and multiple previous operations, there's no question that this remains a very difficult area. Certainly the assessment of pulmonary artery anatomy and pulmonary vascular resistance before operation is of paramount importance.

As indicated one of our patients died one week after operation of residual pulmonary hypertension and, perhaps, in retrospect, was not a good candidate for operation. We don't have any secrets, unfortunately, but we do certainly advocate an absolutely detailed assessment of these children before operation, a very careful assessment of the anatomy and physiology, to try to determine whether they are, in fact, acceptable candidates for transplantation.

And, finally, with regard to the comment of Dr. Busuttil, we have a short follow-up thus far. The patients have been followed a maximum of 45 months, and the long-term renal function remains at this point very much in doubt. I certainly have concerns that we will encounter more renal failure in the future.

And this leads us to be very careful in our immunosuppressive regimen and, certainly, in the level of cyclosporine. After the first year of age, we try to keep the cyclosporine level at 100 or less as determined by high-pressure liquid chromatography.

Whether adjunctive measures will be of any assistance in regard to maintaining renal function is certainly in doubt at this point. But we hope that it will be.

Brush Border Transport of Glutamine and Other Substrates During Sepsis and Endotoxemia

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The effects of severe infection on luminal transport of amino acids and glucose by the small intestine were investigated. Studies were done in endotoxin-treated rats and in septic patients who underwent resection of otherwise normal small bowel. In rats the kinetics of the brush border glutamine transporter and the glutaminase enzyme were examined. In patients the effects of severe infection on the transport of glutamine, alanine, leucine, and glucose were studied. Transport was measured using small intestinal brush border membrane vesicles that were prepared by Mg^{++} aggregation/differential centrifugation. Uptake of radiolabeled substrate was measured using a rapid mixing/filtration technique. Vesicles demonstrated 15-fold enrichments of enzyme markers, classic overshoots, transport into an osmotically active space, and similar 2-hour equilibrium values. The sodium-dependent pathway accounted for nearly 90% of total carrier-mediated transport. Kinetic studies on rat jejunal glutaminase indicated a decrease in activity as early as 2 hours after endotoxin secondary to a decrease in enzyme affinity for glutamine (K_m = 2.23 ± 0.20 mmol/L [millimolar] in controls *versus* 4.55 ± 0.67 in endotoxin, $p < 0.03$), rather than a change in V_{max}. By 12 hours the decrease in glutaminase activity was due to a decrease in V_{max} (222 ± 36 nmol/mg protein/min in controls *versus* 96 ± 16 in endotoxin, $p < 0.03$) rather than a significant change in K_m. Transport data indicated a decrease in sodium-dependent jejunal glutamine uptake 12 hours after endotoxin secondary to a 35% reduction in maximal transport velocity (V_{max} = 325 ± 12 pmol/mg protein/10 sec in controls *versus* 214 ± 8 in endotoxin, $p < 0.0001$) with no change in K_m (carrier affinity). Sodium-dependent glutamine transport was also decreased in septic patients, both in the jejunum (V_{max} for control jejunum = 786 ± 96 pmol/mg protein/10 sec *versus* 417 ± 43 for septic jejunum, $p < 0.01$) and in the ileum (V_{max} of control ileum = 1126 ± 66 pmol/mg protein/10 sec *versus* 415 ± 24 in septic ileum, $p < 0.001$) The rate of jejunal transport of alanine, leucine, and glucose was also decreased in septic patients by 30% to 50% ($p < 0.01$). These data suggest that there is a generalized downregulation of sodium-dependent carrier-mediated substrate transport across the brush border during severe infection, which probably occurs secondary to a decrease in transporter synthesis or an increase in the rate of carrier degradation. The decrease in the number of active brush border carriers for glutamine and the decrease in glutaminase activity, in conjunction with diminished consumption of circulating glutamine demonstrated during sepsis in previous studies, may result in inadequate amounts of this key small intestinal substrate.

THE SMALL INTESTINE plays a key role in the absorption of luminal nutrients. This process not only supplies amino acids for synthetic pathways in the gut mucosa but also provides substrate for the liver and other tissues. Failure to consume adequate amounts of dietary amino acids leads to weight loss, negative nitrogen balance, and erosion of lean body mass. Such consequences may be devastating in critically ill patients who are already catabolic from their underlying disease and who also require greater amounts of dietary protein to maintain nitrogen balance.

Recent studies indicate that the intestinal tract, an organ generally regarded as inactive or quiescent during critical illness, occupies an important physiologic and metabolic position after injury and infection.[1,2] For example the intestinal epithelium functions as a barrier to luminal toxins. This barrier may become threatened or compromised in septic states, leading to an increase in mucosal permeability and subsequent translocation of enteric bacteria and their endotoxins.[3] In addition the gut plays a pivotal role as a processor of circulating substrate, cooperating with the liver and other organs in maintaining amino acid homeostasis. This role in nitrogen metabolism revolves to a considerable extent around the ability of the small intestine to extract large amounts of glutamine from the bloodstream and from the gut lumen.[2,4] Glutamine is the most abundant amino acid in the blood and free amino

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acid pool of the body.[5] Functionally glutamine metabolism by the small intestine (1) provides a major energy source for the gut mucosa to support biosynthetic pathways, (2) provides amide nitrogen that may support nucleotide biosynthesis, and (3) processes nitrogen and carbon from the diet or from the bloodstream for export to other tissues for further metabolism. Glutamine is similarly metabolized whether it enters the mucosal cells across the brush border from the lumen or across the basolateral membrane from the arterial blood, and it is even more important than glucose as an oxidative fuel.[4] This ability of the gut mucosa to extract and metabolize large amounts of glutamine is due to avid transport activity and high levels of the enzyme *glutaminase,* the major enzyme of glutamine metabolism.

We previously reported that glutamine uptake from the bloodstream is diminished in septic patients and in endotoxin-treated rats.[6] Although the consequences of this impairment are unclear, the mechanism by which uptake of circulating glutamine is decreased during sepsis appears to be due primarily to a decrease in glutamine extraction by the bowel and a decrease in the specific activity of mucosal glutaminase, rather than a significant reduction in intestinal blood flow. The changes that occur in brush border substrate transport during septic states are unknown. These changes are important to investigate because certain amino acids, in particular glutamine,[2] may be required for enterocyte growth and function. The purpose of this study was to examine the effects of severe infection on brush border transport of glutamine and other substrates and to study the kinetics of the enzyme *glutaminase* under these circumstances.

Materials and Methods

Studies were done in rodents and in surgical patients. In rats a model of endotoxemia that results in physiologic and physical signs of sepsis was used. In the patients the diagnosis of sepsis was made clinically and confirmed intraoperatively.

Reagents and Chemicals

All chemicals and reagents used were of analytical quality and were purchased from Sigma Chemical Co. (St. Louis, MO). Radiolabeled L-glutamine, L-alanine, L-leucine, and D-glucose were purchased from Amersham (Arlington Heights, IL).

Animal Studies

Male Sprague Dawley rats weighing 250 to 300 g (n = 36, Harlan Sprague Dawley, Indianapolis, IN) were used for the studies. The animals were kept in separate metabolic cages and were fed standard laboratory rat chow (Purina Rodent Chow 5001, Purina Inc., St. Louis, MO) and water *ad libitum.* They were subjected to alternate 12-hour periods of dark and light. Animal care and treatment and study procedures were in accordance with the guidelines of the Animal Care Committee at the University of Florida and the Gainesville Veterans Administration Hospital and the DHEW guide for the care and use of laboratory animals. On the evening before the study, chow was removed from the cages (*ad libitum* intake of water was allowed) and the rats were randomized to receive an intraperitoneal injection of endotoxin (Lipopolysaccharide, *Escherichia coli* 0127:B8, Lot #76F4035, Sigma, 7.5 mg/kg body weight [BW]) or saline vehicle. Batches of six rats were pooled from each group on three separate occasions such that a total of 18 rats were studied in each group. The next morning (12 hours after the saline or endotoxin injection) the animals were anesthetized with ketamine (1 mg/kg BW). The entire length of jejunum was excised, opened along the antimesenteric border, and washed with ice-cold saline (0.9%) solution. The mucosa was then scraped with a glass slide and brush border membrane vesicles (BBMV) were prepared immediately as described below. In separate groups of control and endotoxin-treated rats, jejunal mucosa was obtained 2 and 12 hours after administration of endotoxin or saline. This mucosa was frozen immediately in liquid nitrogen for later determination of glutaminase activity (see below).

Human Studies

Adult surgical patients admitted to the Shands Hospital at the University of Florida of the Gainesville Veterans Administration Hospital were eligible to participate in the study. The studies were approved by the Institutional Review Board at the University of Florida College of Medicine and by the Subcommittee for Clinical Investigation at the Gainesville Veterans Administration Medical Center.

Segments of small intestine were obtained intraoperatively from seven healthy patients and from four septic patients over a 15-month period. The control patients underwent elective abdominal surgery for their primary disease, the treatment of which required resection of small intestine. Four of these patients had a standard right hemicolectomy (two patients with villous adenomas of the cecum, two patients with small carcinomas of the ascending colon). A 10- to 15-centimeter section of ileum was obtained from the surgical specimen and used for transport studies. Portions of jejunum (about 10 cm in length) were obtained from three other patients. One patient had a Roux-en-Y limb of jejunum anastamosed to a pancreatic pseudocyst (for drainage), and a portion of small bowel was obtained at the time the jejunal limb was created. Two other patients had *en bloc* resection of a sigmoid carcinoma and small bowel adherent to the mass.

Ileum was obtained from two septic patients, both of whom had perforation of the cecum and peritonitis. They were treated with right hemicolectomy and ileotranverse colostomy. Jejunum was obtained from two other septic patients, one of whom had *en bloc* resection of a perforated sigmoid diverticular abscess. The other patient had a perforation of a colon cancer with obvious peritonitis that required resection of an adjacent portion of jejunum.

Care was taken in the control patients to study only small bowel specimens from healthy individuals who had no weight loss, normal intake of food before surgery, and no evidence of organ dysfunction. Criteria for inclusion in the septic group were normotension, no evidence of intestinal ischemia or obstruction, previously healthy patients without weight loss who required an emergency operation based on clinical findings, and evidence of peritonitis intraoperatively. Intestine from patients who were not eating normally before the development of abdominal sepsis (*i.e.*, those being NPO [*nulla per os,* nothing by mouth] for greater than 36 hours) were excluded from study, because food intake may affect transport activity.[7,8] Small intestine from septic patients appeared otherwise normal. All surgical procedures were done by the same surgeon (W. W. Souba), and one of us (R. M. Salloum) was present in the operating room each time a portion of small intestine was submitted for study. The specimen was not devascularized until immediately before passing it off the operating table, at which time it was placed promptly on ice and transported immediately to the Surgical/Metabolism Laboratories. The mucosa was rinsed with 0.9% ice-cold saline, scraped with a glass slide, and stored in liquid nitrogen. Brush border membrane vesicles from human small intestinal mucosa were prepared as described below.

Membrane vesicle preparation. Brush border membrane vesicles (BBMVs) were prepared by a Mg^{++} aggregation/differential centrifugation technique.[9,10] For rat studies, the vesicles were prepared immediately after scraping the mucosa. In the patients, the previously frozen mucosa was first thawed. All steps of the preparation were conducted at 0 to 5 C. Briefly each gram of mucosal scrapings was homogenized in 8 mL of 300 mmol/L mannitol and 1 mmol/L N-2 hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES)-TRIS (pH 7.4) buffer with a Polytron homogenizer (Brinkman, setting #6 for 15 seconds). Homogenates from each group were then treated with 100 mmol/L $MgCl_2$/1 mmol/L HEPES/TRIS, to yield a final concentration of 10 mmol/L $MgCl_2$. After stirring for 20 minutes, the homogenate was centrifuged for 5 minutes at 5000*g*. The supernatant containing brush border material was collected and this step was repeated once. The supernatant was then centrifuged at 45,000*g* for 30 minutes. The brush border membrane pellet was resuspended in 350 mmol/L mannitol/50 mmol/L HEPES/TRIS and centrifuged again at 45,000*g* for 30 minutes. The final pellet was resuspended in the same buffer to yield a final protein concentration of 10 to 15 mg/mL. The brush border enzymes alkaline phosphatase and gamma glutamyl transpeptidase were routinely measured to assay for brush border vesicle purity.[11] Protein concentration was determined by the Biorad protein assay (Bio-Rad Laboratories, Richmond, CA) with gamma globulin as the protein standard.

Transport measurements. The uptake of ^{3}[H]-labeled substrate was measured using a rapid mixing/filtration technique.[9,10] In the BBMVs from rats and human ileal specimens, only L-glutamine transport was studied. In BBMVs from human jejunal specimens, the transport of ^{3}H-L-glutamine (^{3}H-Gln), ^{3}H-L-alanine (^{3}H-Ala), ^{3}H-L-leucine (^{3}H-Leu), and ^{3}H-D-Glucose (^{3}H-Glucose) were investigated. For each uptake measurement, 10 μL of BBMVs and 40 μL of the radioactive uptake buffer were placed separately at the bottom of a 12 × 75 polystyrene tube (Fisher Scientific Inc, Pittsburgh, PA). The uptake buffer components were adjusted so that the final concentration mixture contained initial gradients of 120 mmol/L NaCl or KCl and labeled substrate at 10 to 50 μmol/L (micromolar) concentrations. An electronically controlled device was used to initiate the reaction by rapidly vibrating the tube.[10] After the prescribed reaction period (15 seconds to 2 hours), 1 mL of ice-cold stop buffer (150 mmol/L NaCl/10 mmol/L HEPES/TRIS, pH 7.5) was added to quench the reaction. The quenched reaction mixture was then filtered using a prewetted and chilled 0.45-μm membrane filter (Gelman Scientific product no. 63068 Gn-6). The membranes were washed once with 5 mL of stop buffer and then dissolved in Aquasol Scintillation cocktail (Dupont, NEN Research Products, Boston, MA). The radioactivity trapped by the vesicles was measured by liquid scintillation counting. Values for nonspecific retention of the radioactivity by the filter and the vesicles were obtained from time zero uptakes and were subtracted from the total filter radioactivity. The radioactivity was converted to units of uptake and expressed as picomoles per milligram protein per time. Uptake was measured in the presence and absence of sodium with potassium as the control cation.

Statistical analysis. All data are expressed as mean ± standard error. Data were compared using the unpaired two-tailed Student's t test (MacIntosh Plus Computer, Statview 512 Statistical Program, Apple Computers, Cupertino, CA). A probability value less than 0.05 was considered statistically significant.

Results

Brush Border Purification

The purity of the brush border membranes was ascertained by determining the activities of the brush border marker enzymes alkaline phosphatase and gamma-glutamyl transpeptidase. Both enzymes showed a 14- to 16-

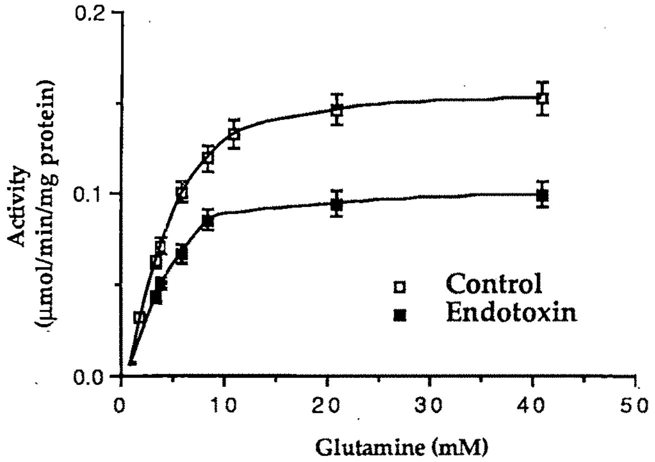

FIG. 1. Saturation plot of jejunal glutaminase activity in control and 12-hour endotoxin-treated rats. The activity of phosphate-dependent glutaminase was measured at various glutamine concentrations ranging from 1 to 40 mmol/L as described in the Methods section. Enzyme activity is plotted *versus* glutamine concentration.

fold enrichment in vesicles from control and endotoxin-treated rats and from normal and septic patients when compared with the crude homogenate (in rat jejunum, 515 ± 32 nmol/mg protein/minute *versus* 7401 ± 676 nmol/mg protein/min in the original homogenate and the BBMV suspension, respectively, and in human jejunum, 416 ± 62 *versus* 6652 ± 598, $p < 0.0001$).

Transport Characteristics

In both human and rat BBMVs, glutamine transport was measured in the presence and absence of NaCl (with KCl substitution). Transport was significantly higher in the presence of sodium and demonstrated classical overshoots. Sodium-dependent carrier-mediated transport accounted for 90% of total carrier-mediated uptake. Hence sodium-dependent glutamine transport data are presented in the results. Sodium-independent transport was not altered by severe infection. Osmolarity studies (data not shown) showed uptake into an osmotically active intravesicular space. Vesicular size was similar in all compared groups, as evidenced by the 2-hour equilibrium values of substrate uptake by the BBMVs.

Rat Studies

Effects of endotoxin. Rats receiving endotoxin developed decreased physical activity, conjuctivitis, and piloerection. Saline-treated animals appeared normal.

Glutaminase kinetic parameters. The activity of phosphate-dependent glutaminase was measured at various glutamine concentrations ranging from 1 to 40 mmol/L, using a fluorometric assay similar to the one described by Pinkus and Windmueller.[12] In rats studied 12 hours after endotoxin treatment, data in the form of a saturation plot (activity *versus* glutamine concentration) is shown in Figure 1. The data were linearized, generating an Eadie-Hofstee plot (Fig. 2), by plotting enzyme activity *versus* activity/glutamine concentration. The K_m (a measure of enzyme affinity for the glutamine) is the negative of the slope of the line and the V_{max} (a measure of the number of active enzyme molecules) is the activity of the enzyme at infinite substrate concentration. This linear relationship is summarized by the following equation:

$$V = V_{max} - K_m V/[Gln]$$

where transport velocity V is measured on the y-axis, V/[GLN] is measured on the x-axis, K_m is the slope of the line, and V_{max} is the y-intercept. At the 12-hour time point, the K_m was not different between both groups, but there was a significant decrease in V_{max} in the endotoxin-treated rats (Fig. 2, Table 1). In contrast, the 2-hour endotoxin-treated rats showed a significant increase in K_m, indicating a decrease in the affinity of the phosphate-dependent glutaminase enzyme for glutamine at this time point (Fig. 3, Table 1).

Glutamine uptake rates. The sodium-dependent timecourse of ^{3}H-Gln by rat jejunal BBMVs is shown in Figure 4. The BBMVs from endotoxin-treated rats had significantly decreased glutamine uptake compared with control rats.

Glutamine transport kinetics. Glutamine transport rates were measured as a function of concentration (10 µmol/L − 10 mmol/L) in the presence of 120 mmol/L NaCl or KCl. Incubations were performed for 10 seconds. Total glutamine uptake velocity (V^{Total}) was resolved into three transport pathways:

$$V^{Total} = V^{D} + V^{Na\text{-}dep} + V^{Na\text{-}indep}$$

$$V^{K} = V^{Na\text{-}indep} + V^{D}$$

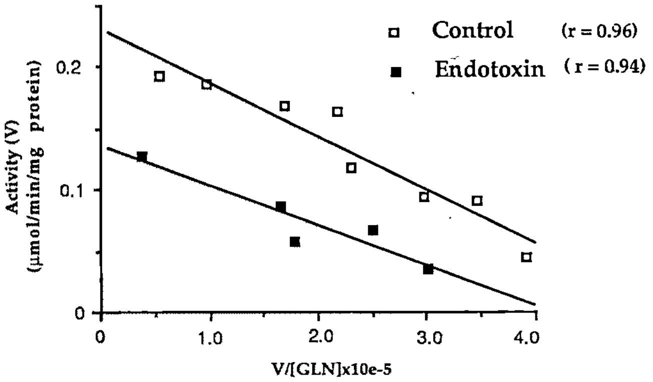

FIG. 2. Eadie-Hofstee plots of saturable glutaminase activity in control and 12-hour endotoxin-treated rats. The activity of phosphate-dependent glutaminase was measured at various glutamine concentrations ranging from 1 to 40 mmol/L as described in the Methods section. Enzyme activity is plotted against activity/[GLN]. Plots shown are representative of data generated from assays performed on three separate control and endotoxin-treated rat mucosal preparations, each done in triplicate. The slopes of the lines indicated a similar K_m, while y-intercepts indicate a decrease in V_{max} in endotoxin-treated rats.

TABLE 1. *Glutaminase Kinetics in Control and Endotoxin-Treated Rats*

	2 Hours After Endotoxin		12 Hours After Endotoxin	
Group	K_m (mmol/L)	V_{max} (nmol/mg/min)	K_m (mmol/L)	V_{max} (nmol/mg/min)
Control	2.23 ± 0.20	146 ± 19	3.67 ± 1.05	222 ± 36
Endotoxin	4.55 ± 0.67*	163 ± 7	2.20 ± 0.50	96 ± 16*

Data = mean ± SEM of three separate experiments done in triplicate. * $p < 0.03$ *versus* control.

such that V^{Total} refers to the total uptake in the sodium buffer, $V^{Na\text{-}dep}$ is the carrier-mediated sodium-dependent uptake, $V^{Na\text{-}indep}$ refers to carrier-mediated sodium-independent uptake, V^D is the passive diffusional uptake, and V^K is the uptake of glutamine in the absence of sodium, using potassium (K^+) as the control cation. The sodium-dependent component of total uptake, which represented nearly 90% of total uptake, is obtained from the following equation:

$$V^{Na\text{-}dep} = V^{Total} - V^K$$

An Eadie-Hofstee plot (Fig. 5) is generated by plotting $V^{Na\text{-}dep}$ *versus* $V^{Na\text{-}dep}/[Gln]$ according to the following linear equation:

$$V^{Na\text{-}dep} = V^{max} - K^m\ V^{Na\text{-}dep}/[Gln]$$

where K_m represents the apparent affinity of the transporter and V_{max} is the maximal uptake velocity. The mean kinetic constants from three separate experiments done in triplicate are shown in Table 2. Endotoxin treatment resulted in a significant decrease in V_{max}, but no change in K_m (Fig. 5).

Human Studies

Glutamine uptake rates. The time course of sodium-dependent jejunal transport is shown in Figure 6. The overshoot phenomenon was observed in both groups of patients and the 2-hour equilibrium values were the same, indicating similar vesicular size. Transport of ^{3}H-Gln by BBMVs was significantly decreased in the septic patients.

Glutamine transport kinetics. Glutamine transport rates were measured as a function of glutamine concentration (10 μmol/L to 10 mmol/L) in the presence of 120 mmol/L NaCl or KCl. Incubations were performed for 10 seconds. Total glutamine uptake velocity (V^{Total}) was resolved into the three transport pathways as described above. Eadie-Hofstee plots for both jejunal and ileal transport were generated by plotting $V^{Na\text{-}dep}$ *versus* $V^{Na\text{-}dep}/[Gln]$ to generate the lines shown in Figures 7 and 8. The apparent K_m for the sodium-dependent transporter in both the jejunum and ileum was not altered by the septic state. However the V_{max} of the transporter in septic patients was significantly decreased compared with controls, consistent with a decreased number of active transport molecules. Kinetic data are shown in Table 3.

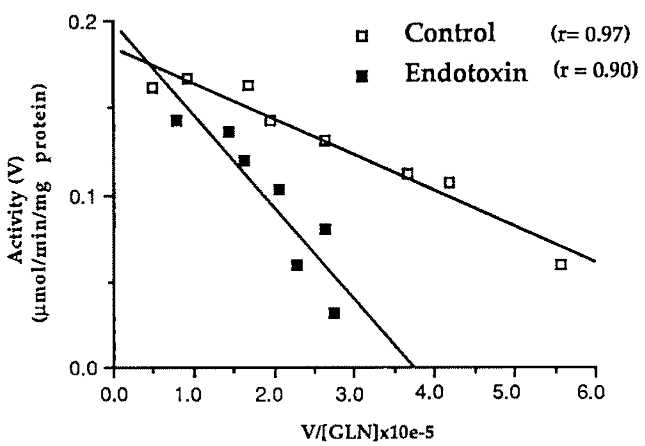

FIG. 3. Eadie-Hofstee plots of saturable glutaminase activity in control and 2-hour endotoxin-treated rats. The activity of phosphate-dependent glutaminase was measured at various glutamine concentrations ranging from 1 to 40 mmol/L as described in Methods. Enzyme activity is plotted against activity/[GLN]. Representative plots are shown. The slopes of the lines show an increase in K_m in endotoxin-treated rats, indicating a decrease in enzyme affinity. The V_{max} (y-intercept) was not affected.

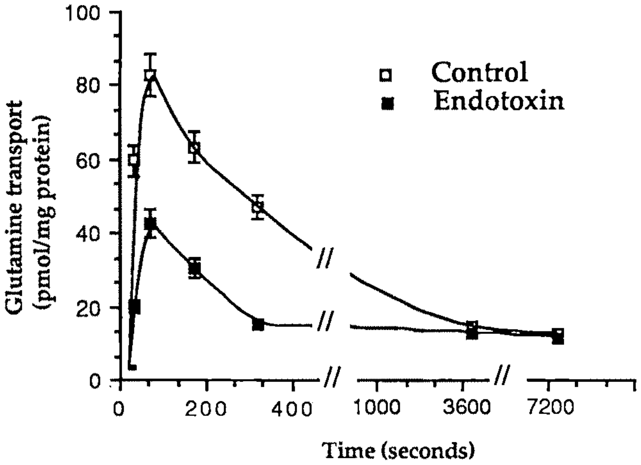

FIG. 4. Time course of glutamine uptake by BBMVs from control and 12-hour endotoxin-treated rats. BBMVs were incubated with 50 μmol/L glutamine uptake buffer as described in Methods. The figure is a representative time course of three assays performed separately from three different BBMVs preparations. Each data point represents mean ± SEM of triplicate measurements. When not shown the error bars are contained within the symbol. BBMV, brush border membrane vesicles.

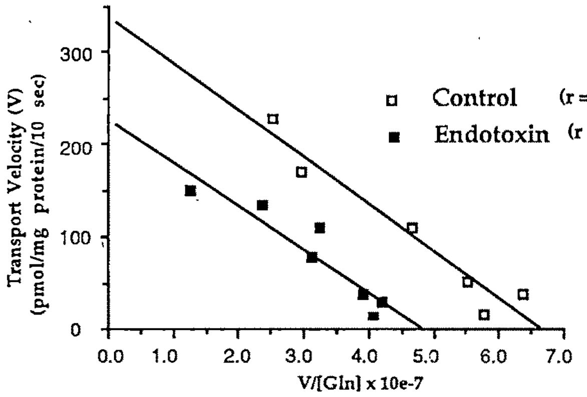

FIG. 5. Eadie-Hofstee plots of glutamine transport in BBMVs from control and 12-hour endotoxin-treated animals. BBMVs were incubated with varying concentrations of glutamine ranging from 10 μmol/L to 10 mmol/L for a period of 10 seconds. Sodium-dependent glutamine uptake was determined as described in Methods and uptake velocity was plotted as a function of velocity/[glutamine]. The y-axis intercept represents maximal transport velocity (V_{max}) and negative slope corresponds to the apparent K_m (transporter affinity). Plots shown are representative of data generated from transport assays performed on three separate control and endotoxin-treated rat BBMV preparations, each done in triplicate.

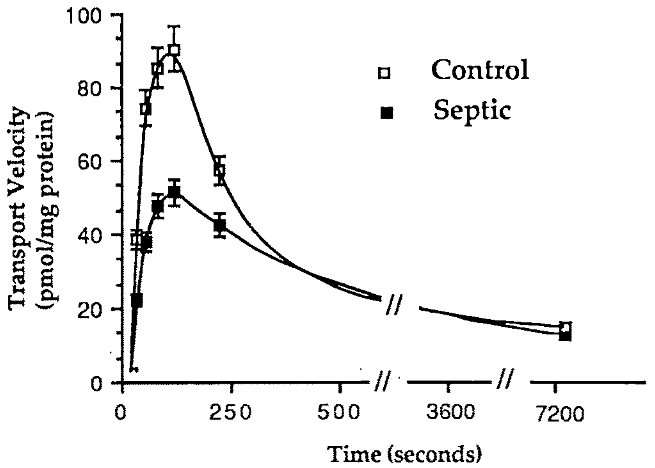

FIG. 6. Time course of glutamine uptake by jejunal BBMVs from control and septic patients. BBMVs were incubated in 50 μmol/L glutamine as described in Methods. The figure is a representative time course of three assays performed separately from three different BBMVs preparations from each of three control and two septic patients. Each data point represents the mean ± SEM of triplicate measurements. When not shown, the error bars are contained within the symbol.

Effects of sepsis on other transporters. To determine the specificity of the effects of sepsis on brush border transport, the total uptake ($V^{Na\text{-}dep} + V^{Na\text{-}indep} + V^{D}$) of ^{3}H-alanine, ^{3}H-leucine, and ^{3}H-glucose by human jejunal BBMVs was also measured. The uptake of all substrates was significantly decreased in the septic patients (Fig. 9, Table 4).

Discussion

Small intestinal brush border transport of glutamine and other substrates was studied in septic patients and in endotoxin-treated rats to gain further knowledge of the changes in gut fuel use that occur during severe infection. The results demonstrate similar decreases in brush border glutamine transport in septic humans and in rodents receiving *E. coli* lipopolysaccharide (LPS). Additional studies in jejunal BBMVs from healthy and septic patients indicated a generalized decrease in amino acid and glucose transport during severe infection.

Endotoxicosis is an accepted laboratory model of sepsis[13]; animal[14] and human[15] studies demonstrate that a single dose of endotoxin evokes many of the physiologic responses observed in severe bacterial infection. The rat endotoxin model we used is a reproducible model that has clinical relevance because septic patients develop the same impairment in gut glutamine metabolism as do entotoxin-treated rats. In addition, the regulation of these transport alterations (*e.g.*, by cytokines) at the molecular level can be studied. Such knowledge of metabolic regulation is essential for treatment strategies to be envisioned and implemented.

TABLE 2. *Jejunal Brush Border Glutamine Transport Kinetics in Control and Endotoxin-Treated Rats*

Group	K_m (μmol/L)	V_{max} (pmol/mg prot/10 s)
Control	492 ± 35	325 ± 12
Endotoxin	488 ± 16	214 ± 8*

Data = mean ± SEM of three separate experiments done in triplicate.
* $p < 0.0001$ *versus* control.

Luminal amino acids are transported across the brush border membrane of the small intestine by several well-

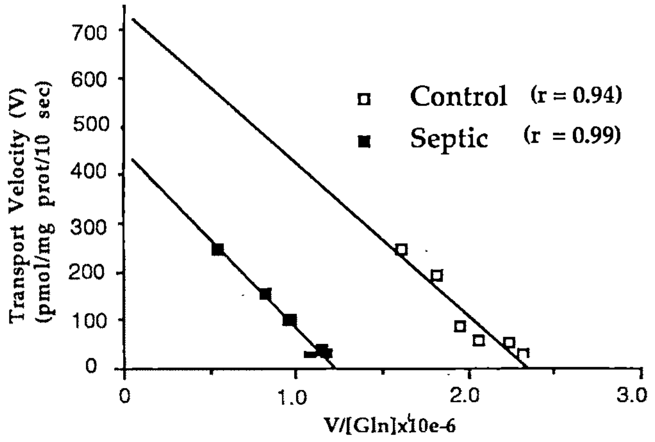

FIG. 7. Representative Eadie-Hofstee plot of glutamine transport in jejunal BBMVs from control and septic patients. BBMVs were incubated as described in Methods. The plot is representative of data generated from three assays performed on three separate control and two septic BBMV preparations, each done in triplicate.

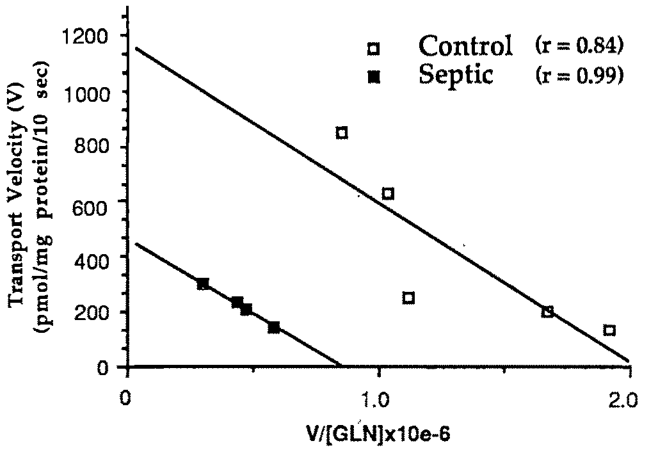

FIG. 8. Representative Eadie-Hofstee plot of glutamine transport in ileal BBMVs from control and septic patients. BBMVs were incubated as described in Methods. The plot is representative of data generated from three assays performed on four separate control and two septic BBMV preparations, each done in triplicate.

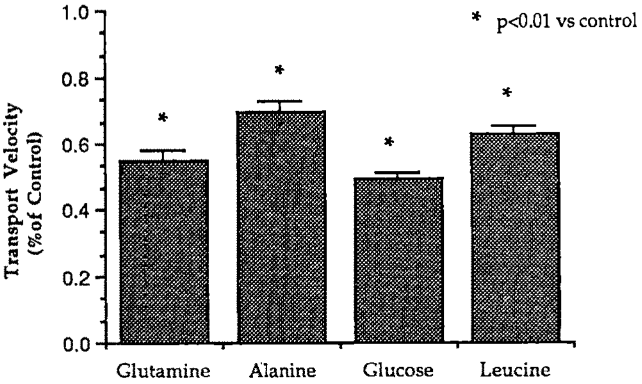

FIG. 9. Total substrate transport in jejunal BBMVs from septic patients expressed as a percentage of transport in jejunal BBMVs from healthy controls. BBMVs were incubated in 50 μmol/L each of glutamine, alanine, glucose, and leucine for a period of 10 seconds as described in Methods. The bar graph is the mean of three assays performed separately in triplicate on BBMVs preparations from each of two control and two septic patients. Each data point represents the mean ± SEM of triplicate measurements.

described transport systems.[16,17] In general translocation of luminal substrates into the cytoplasm of the enterocyte occurs by three separate pathways: a sodium-dependent route, a sodium-independent pathway, and by diffusion, which reflects the permeability of the membrane. The sodium-dependent route is usually the dominant pathway. In the case of glutamine, the jejunal brush border carrier for glutamine has not been fully characterized but may bear some resemblance to system N.[18,19] The carrier for alanine, however, is principally the sodium-dependent system A,[17] whereas leucine is mainly transported by the sodium-independent system L.[17] Glucose uptake from the lumen also occurs through a sodium dependent co-transporter.[20] Under normal circumstances the rate of transporter synthesis is balanced by the rate of carrier degradation such that a steady state exists and the number of copies of transporter molecules on the brush border is constant.

Three principal factors determine the uptake of amino acids and glucose across the brush border. They are the quantity of luminal substrate available to the epithelial cells, the capacity of the individual cells to translocate the compound into the intracellular compartment, and the capacity of the cell to use intracellularly available substrate. In the current investigations, we focussed on the intrinsic activity of the transport machinery as well as on the activity of the glutaminase enzyme. The use of plasma membrane vesicles to assess brush border substrate transport activity offers several advantages over other approaches. Alterations in membrane transport activity are preserved during the preparation of vesicles[9] and transport activity can be evaluated apart from other confounding influences such as metabolism and trans-stimulation/inhibition. The decrease in glutamine transport activity we observed was not the result of nonspecific differential effects of endotoxin on vesicle membrane permeability or transport characteristics, as we did not observe alterations in sodium-independent glutamine uptake (data not shown). In addition, BBMVs from endotoxin-treated rats and septic patients demonstrated enrichments and overshoots, indicating vesicle purity and functionality.

Severe infection did not change the affinity of the Na^+-dependent cotransporter for glutamine (the apparent K_m was unchanged) but the $V_{max}{}^{Na}$ decreased to about one

TABLE 3. *Brush Border Glutamine Transport Kinetics in Control and Septic Patients*

	Jejunum		Ileum	
Group	K_m (μmol/L)	V_{max} (pmol/mg/10 s)	K_m (μmol/L)	V_{max} (pmol/mg/10 s)
Control	729 ± 84	786 ± 96	513 ± 46	1126 ± 66
Septic	619 ± 92	417 ± 43*	552 ± 10	415 ± 24†

Data = mean ± SEM of two separate experiments done in triplicate.
* $p < 0.01$; †$p < 0.001$ *versus* control.

TABLE 4. *Brush Border Jejunal Substrate Transport in Control and Septic Patients (pmol/mg protein/10 s)*

Group	Glutamine	Alanine	Leucine	Glucose
Control	36.1 ± 1.5	49.5 ± 6.9	83.7 ± 7.8	193.1 ± 9.6
Septic	19.9 ± 1.9*	34.4 ± 1.8*	52.1 ± 2.8*	94.3 ± 3.9*

Data = mean ± SEM of two separate determinations done each in triplicate.
* $p < 0.01$ *versus* control.

half of that observed in control rats and healthy humans. In addition, total transport of alanine, leucine, and glucose was diminished. Interestingly kinetic measurements in animals studied 4 hours after endotoxin treatment showed that glutamine transport was actually increased at this early timepoint (data not shown). Thus it appears that the gut mucosal response to endotoxemia may be biphasic in nature, with an early increase in transport activity followed by a later decrease in the number of active transporters on the cell surface. Whether this change in carrier activity is the result of reduced transporter synthesis or increased transport degradation (or both) is not clear from the present study. Interestingly, recent work by von Allmen and colleagues[21] demonstrated that mucosal protein synthesis is increased 16 hours after induction of fecal peritonitis by cecal ligation and puncture. Protein content of the bowel was unchanged, indicating a concomittant increase in protein breakdown in the mucosa or export of newly synthesized proteins. Thus small intestinal protein synthesis may be reprioritized during severe infection. At a time when energy use is at a premium and protein synthetic requirements must be prioritized, the mucosa may redirect the flow of energy to more acute synthetic needs (such as acute phase protein synthesis) at the expense of transport-related protein synthesis. Simultaneously the gut uses increased amounts of glucose,[22] its alternate fuel. In contrast to the gut, a decrease in the intrinsic glutamine transport activity does not occur in the hepatocyte of endotoxin-treated rats (Souba et al., unpublished observations), and synthesis of the glutamine carrier in pulmonary endothelial cells is actually increased by endotoxin.[23] Thus whether the bowel becomes purposefully 'subservient' to the glutamine needs of the liver and lungs requires further elucidation.

One important question raised by these studies is whether luminal transport activity can be stimulated in septic patients by providing luminal nutrients. Evidence exists that the activity of brush border nutrient transporters can be regulated by their respective substrates.[7] Diamond and Karasov[8] studied the influence of diet on the adaptive regulation of intestinal nutrient transporters. They suggested that fluctuations in transport activity are based on trade-offs among factors such as cost of transporter synthesis and nutrient requirements. Their work indicated that the basal rate of luminal transport can be up-regulated by dietary substrate. This observation may be important in critically ill patients, as it suggests that enteral nutrition may help offset the decrease in luminal transport activity that occurs during severe infection. Maintenance of transport function may also be important in such individuals, as dietary substrate can profoundly influence protein synthesis in the gut mucosa. Furthermore it is clear that enteral feedings improve outcome in critically ill patients,[24] an event that may be related to reprioritization of hepatic protein synthesis.[25] Early enteral nutrition can also blunt the catabolic response to burn injury and help preserve mucosal integrity.[26]

The amino acid glutamine has received considerable attention in the past decade, partly because of new knowledge demonstrating that its metabolism changes markedly during critical illness and also because of studies that suggest that it may be a conditionally essential amino acid. Supplemental glutamine, for example, can improve intestinal morphometrics and improve survival in animals receiving whole abdominal radiation[27,28] or chemotherapy.[29] Thus the relationship between the septic insult and the metabolic derangements may be more than casual. In view of the data presented in this study in conjunction with recent work, one might ask whether the provision of glutamine-enriched diets could stimulate mucosal metabolism and improve gut function during septic states.

We recognize that severe infection may result in changes in the mucosal microcirculation that may directly affect substrate transport by the gut epithelium. Such alterations might be mediated by endothelial cells or inflammatory cells. Certainly, like the changes in permeability that occur during endotoxemia, the regulation of the changes in substrate use that occur is likely to be complex and multifactorial. Regardless of the specific mechanisms involved, it is clear that sepsis results in a marked inability of the bowel to consume glutamine and other nutrients. The consequences of this impairment as well as its natural history with regard to progression and resolution require further study.

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DISCUSSIONS

DR. EDWIN DEITCH (Shreveport, Louisiana): As you have just heard, the authors have presented data indicating that brush-border glutaminase activity and the transport of glutamine is decreased, and this decrease appears to be due primarily to quantitative decreases in the amount of glutaminase enzyme or glutamine transporters and not due to functional alterations of these systems. That is, what is there works. The problem is that what is there is reduced in number.

This basic work has very important clinical implications because we have information indicating that glutamine has several unique and important functions. We know that glutamine, rather than glucose, is the primary nutrient to the small intestine and that maintenance of intestinal structure and function may depend significantly on glutamine availability.

In addition we know that glutamine is an optimal and essential nutrient that's required for the immune system to function. Thus one clinical implication of these results is that the net effect of these impairments in intestinal glutamine metabolism and transport may result in an inadequate availability of glutamine to support optimally intestinal barrier functions during stress states.

This assumption fits in very well with the previously published data from my laboratory looking at endotoxin and barrier function of the intestine. We have shown, and others have as well, that endotoxin in stress states can lead to gut barrier failure and potential lethal gut origin septic states.

Would the authors comment on the potential therapeutic role of glutamine administration? I ask this question because the second implication of this work is that because the glutaminase and glutamine transporters that are present function normally, it may be possible to meet the cells' glutamine needs by increasing substrate availability.

In other words, it may be possible to compensate for these defects in glutamine transport by increasing the amount of exogenously supplied glutamine.

Because the physiology of glutamine metabolism and transport *in vivo* is incredibly complex and is influenced by more variables than can be addressed by *in vitro* studies, I would like to ask the following questions.

In vivo glutamine is transported to the cells from both the blood *via* the basal lateral membrane as well as to the intestine across the brush border. Thus would you put your data on luminal transport into perspective with the information you have generated on basal lateral transport? This question is potentially important because, especially in a nonfed state, the majority of glutamine transported to the epithelial cells may come from the blood.

There are two glutaminases. A phosphate-independent glutaminase, which is in the brush border, and a membrane-dependent glutaminase, which is in the mitochondria.

Because mitochondria glutaminase activity may be more important physiologically than brush-border glutaminase *in vivo* under certain circumstances, do you have any information on whether mitochondrial glutaminase activity is altered?

This question may be important because, methodologically, when the vesicles are formed from homogenized mucosa, it is possible that it could contain or have been contaminated with mitochondria or mitochondrial fragments.

Thus do you have any data documenting whether brush-border glutaminase was contaminated with mitochondrial glutaminase?

Last because glucose, alanine, and leucine transport also were decreased, it appears that the observations of glutamine transport are not specific. Instead they may reflect a global and nonspecific change in membrane transport. Would you speculate on the mechanisms underlying these changes?

DR. J. W. ALEXANDER (Cincinnati, Ohio): I think it's fairly clear from Dr. Copeland's very lucid presentation what the implications of this paper are. That is why it's so difficult to maintain nutritional status by either the enteral or parenteral route in individuals who are septic.

I'll make my discussion relatively short by focusing on four areas of questions, one of which is methodologic. And that is partly because of my ignorance. It would be interesting for all of us to know whether there could be some methodologic variance of this study because of differences in potential fragility of the vesicles as they are prepared. It could be, as an example, that they are more fragile in the septic state. They could create a methodologic error decreasing the apparent transport.

They have shown clearly that glutamine and glucose and aminoacid uptake is decreased, and I would like to know if there is any evidence of decrease of other alternative fuels for the gut, such as short chain fatty acids, ketoacids, or even lipids.

Next is there anything that might reverse this process? This has tremendous therapeutic implications for the septic patient who is trying to be fed. As we know in normal individuals, there are a variety of things that can increase uptake of the intestines of a variety of substances, particularly nutrients. These include dietary substrates themselves and a variety of hormonal substances such as bombesin and perhaps growth hormone and certainly some of the prostaglanden analogues, particularly of the E series.

Finally, as Dr. Deitch has indicated in his discussion, there is a great amount of data that have accumulated related to transport of endotoxin across the gut, and some of this will be discussed in my paper tomorrow.

It is clear that transport of endotoxin across the intestinal barrier is increased following a variety of injurious stimuli. In the paper Drs. Copeland and Souba have indicated that in fact glutamine uptake increased at 4 hours. Thus there is a definite difference related to the time of the injection of endotoxin, and as to whether uptake is increased or decreased.

Is there an explanation for this change in the transport of these substances? And in particular, might there be a decrease in endotoxin later? Of even more interest, does endotoxin regulate the changes in these transport mechanisms?

DR. JOSEF FISCHER (Cincinnati, Ohio): This is a nicely done and presented continuation of work that shows the critical nature of glutamine to enterocytes.

May I have my first slide, please?

This is some work that really doesn't have much to do with sepsis but shows isolated enterocytes in a different situation, which shows that you can increase the output of protein synthesis in gut mucosa and isolated enterocytes in a control situation and also sometimes substitute for glutamine with various other aminoacids.

We agree with the premise that glutamine is—and much of the work that Souba and Copeland have done shows this—an essential fuel.

They have raised a number of other issues. One of the issues is whether glutaminase is a good marker for overall metabolizing capacity by the intestine. Glutaminase is a funny enzyme, to which Dr. Deitch has already alluded. It exists in liver, brain, and kidney, and it's a very small enzyme. It only weighs about 65 kd. And so there are difficulties in isolation.

Many laboratories use antibody-binding techniques to measure the activity of glutaminase, which is a sure sign that the standard techniques that most of us use to measure antibody activity really don't work very well.

Dr. Alexander has already raised a question of methodology. Whenever I see changes in km or the actual structure or the affinity of an enzyme, I have to wonder whether there is a methodologic problem, although the data in this manuscript seemed pretty good that they are actually seeing an alteration in km.

Without putting any words in the authors' mouths, they have a very attractive hypothesis that decreasing glutamine uptake and decreasing glutaminase results in greater permeability supporting the noxious effects of sepsis by translocation of either bacteria or other products into the gut.

Unfortunately there are scenarios other than endotoxin and sepsis in which this has been tested, and the data are not consistent. Newsholm, for example, has found that in burns—in which I think everybody agrees that there is increased permeability of material across the gut—despite the fact that everybody agrees that in the burn model translocation occurs, there is increased glutamine use and an increased measured glutaminase activity. So there is disparity, at least in the model they used, although it's a little longer term.

The second issue, and this is referred to in the manuscript, is studies by one of our own residents, Dan van Allmen, who found that in sepsis—and this is a cecal ligation and puncture model—protein synthesis by isolated enterocytes at 16 hours actually increases. Now some of these proteins are gut hormones, which we think are exported to the liver, that stimulate the liver for sepsis. So there is that nice relationship. And as the authors have already noted, this is biphasic. And early studies show that these are stimulated.

I would like to ask three questions. First you have studied the vesicle transport in the brush border but not in the basal lateral membrane. What is the relative importance of the basal lateral membrane? I think Ed Deitch already referred to this. And is it possible that there is a disparity between these two types of transport?

The second is a technical question. I assume that their control patients, the seven control patients, were fasted overnight and they took the special pains to make certain that the septic patients were not fasted for any longer than 36 hours. And 36 hours seems like a relatively short time, but in fact it's a relatively long time to the intestine, in which the turnover is 36 hours.

Do they have any data in control patients who have been fasted for 8, 12, 24, 36, and 48 hours? Did the difference in time between the control patients and the septic patients have any influence on the results.

This is fascinating work with important clinical implications.

DR. W. W. SOUBA (Closing discussion): Dr. Deitch asked what happens to transport across the basolateral membrane. We do not know the answer to that question because the basolateral prep is more difficult to work with and the percentage contamination from other organelles is higher. Although we previously reported that uptake of glutamine from the bloodstream is decreased in septic patients, this could be secondary to a decrease in intracellular metabolism rather than a direct reduction in basolateral transporters. Most likely, however, transport across the blood facing membrane is also diminished.

It is important to differentiate between transport and metabolism. One phenomenon involves translocation of glutamine into the cell from the gut lumen from the bloodstream. The second, metabolism, involves the hydrolysis of the glutamine molecule by the glutaminase enzyme, which is mitochondrial bound.

The regulation of these changes is poorly understood. The regulation may be biphasic in nature in that early on transport may be increased (4 hours) with a later decrease in transport activity. Perhaps the cell is reprioritizing protein synthesis during severe infection.

Dr. Alexander asked about methodology. The vesicles from both septic and normal patients appeared to be functional with good vesicle integrity based on similar 2-hour equilibrium points, similar enrichments, and identical diffusion capacities. In terms of recovery from these insults, that information is unknown.

With regard to Dr. Fischer's questions, we are using a human enterocyticlike cell line that allows us to study direct effects of regulators independent of factors such as bloodflow and cell-cell interactions. We are aware of Dr. Van Allman's work from Cincinnati, which shows that protein synthesis in the gut mucosa of septic animals is increased at the 16-hour time point. This fits with the idea that the cell may be redirecting synthetic properties.

Whether decreased glutamine availability results in mucosal injury is unknown. Certainly in other models of bowel injury, glutamine can accelerate healing.

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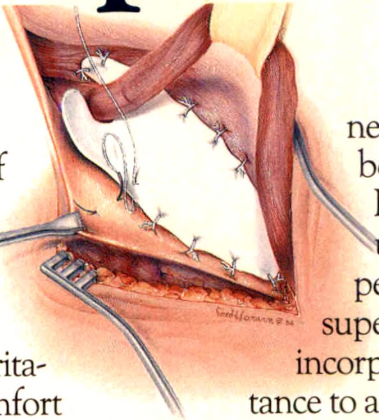

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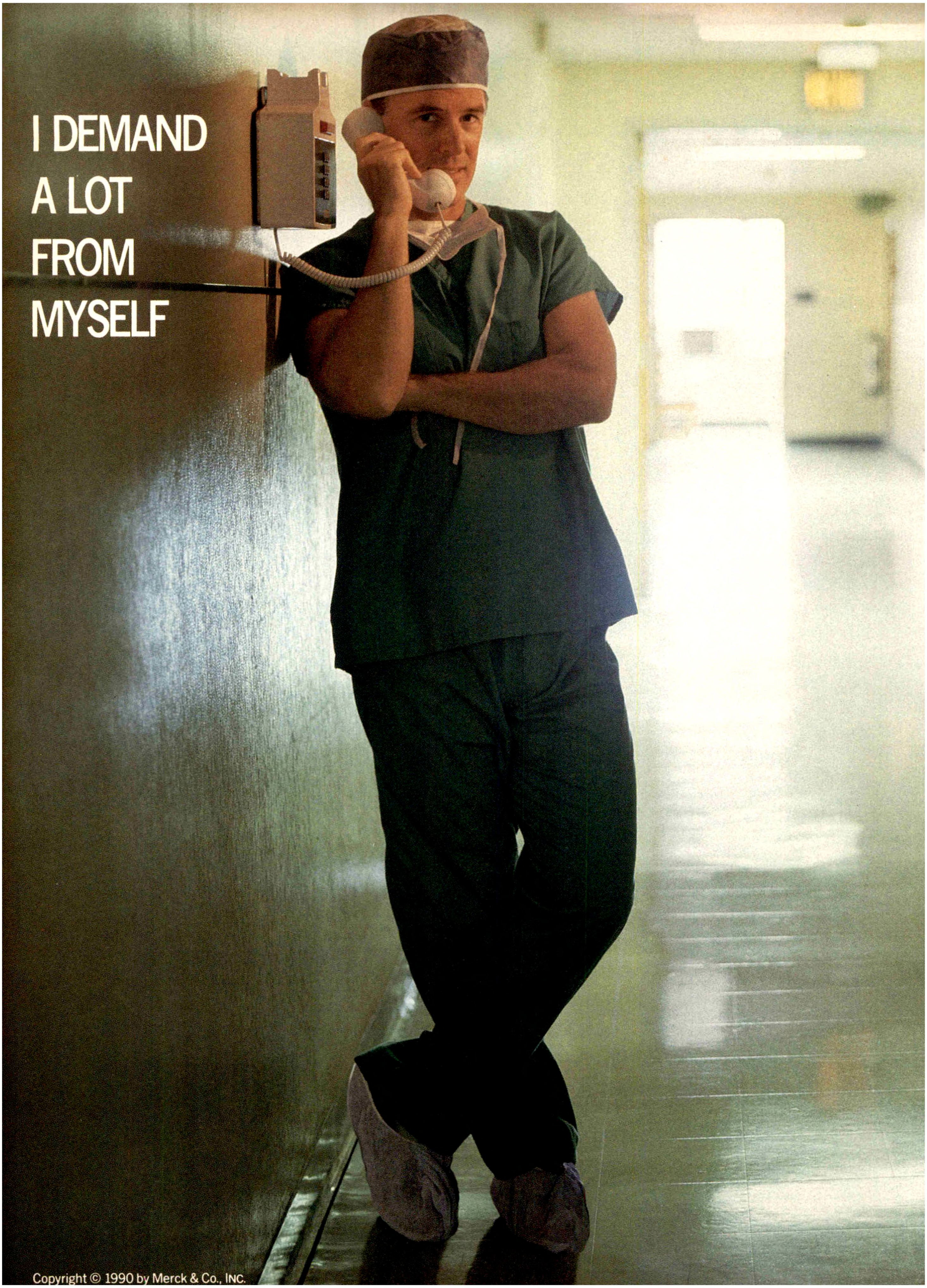

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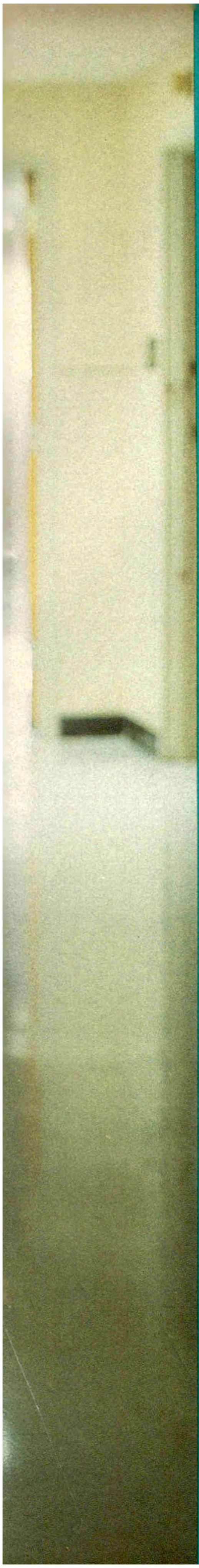

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clinical experience*
...broad coverage
of important
aerobes and anaerobes,
including the
B. fragilis group
...used in over 14 million patients.

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[†] *in vitro* activity against indicated aerobes and anaerobes

MEFOXIN is contraindicated in patients who have shown hypersensitivity to cefoxitin and the cephalosporin group of antibiotics.

MEFOXIN is not active *in vitro* against most strains of *Pseudomonas aeruginosa* and enterococci (e.g., *Streptococcus faecalis*) and many strains of *Enterobacter cloacae*. Methicillin-resistant staphylococci are almost uniformly resistant to MEFOXIN.

*in infections caused by indicated organisms at indicated sites

Please see following page for a Brief Summary of Prescribing Information

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MEFOXIN® IV/IM

(CEFOXITIN SODIUM | MSD)

†*in vitro* activity against indicated aerobes and anaerobes

Indications and Usage: *Treatment*—Serious infections caused by susceptible strains of the designated microorganisms in the following diseases:
LOWER RESPIRATORY TRACT INFECTIONS, including pneumonia and lung abscess, caused by *Streptococcus pneumoniae*, other streptococci (excluding enterococci, e.g., *Strep. faecalis*), *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Escherichia coli, Klebsiella* species, *Hemophilus influenzae*, and *Bacteroides* species.
GENITOURINARY INFECTIONS. Urinary tract infections caused by *E. coli, Klebsiella* species, *Proteus mirabilis*, indole-positive *Proteus* (which include the organisms now called *Morganella morganii* and *Proteus vulgaris*), and *Providencia* species (including *Providencia rettgeri*). Uncomplicated gonorrhea due to *Neisseria gonorrhoeae* (penicillinase and non-penicillinase producing).
INTRA-ABDOMINAL INFECTIONS, including peritonitis and intra-abdominal abscess, caused by *E. coli, Klebsiella* species, *Bacteroides* species including the *B. fragilis* group,* and *Clostridium* species.
GYNECOLOGICAL INFECTIONS, including endometritis, pelvic cellulitis, and pelvic inflammatory disease, caused by *E. coli, N. gonorrhoeae* (penicillinase and non-penicillinase producing), *Bacteroides* species including the *B. fragilis* group,* *Clostridium* species, *Peptococcus* species, *Peptostreptococcus* species, and group B streptococci.
SEPTICEMIA caused by *Strep. pneumoniae, Staph. aureus* (penicillinase and non-penicillinase producing), *E. coli, Klebsiella* species, and *Bacteroides* species including the *B. fragilis* group.*
BONE AND JOINT INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase producing).
SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase producing), *Staph. epidermidis*, streptococci (excluding enterococci, e.g., *Strep. faecalis*), *E. coli, P. mirabilis, Klebsiella* species, *Bacteroides* species including the *B. fragilis group,* Clostridium* species, *Peptococcus* species, and *Peptostreptococcus* species.
Although appropriate culture and susceptibility studies should be performed, therapy may be started while awaiting these results. Cefoxitin is not active *in vitro* against most strains of *Pseudomonas aeruginosa* and enterococci (e.g., *Strep. faecalis*) and many strains of *Enterobacter cloacae*. Methicillin-resistant staphylococci are almost uniformly resistant to cefoxitin.
Prevention—Prophylactic use in surgical procedures (e.g., hysterectomy, gastrointestinal surgery, cesarean section, transurethral prostatectomy) classified as contaminated or potentially contaminated or in patients in whom subsequent infection at the operative site would present a serious risk, e.g., prosthetic arthroplasty. MEFOXIN usually should be given ½ to 1 hour before surgery and should usually be stopped within 24 hours since continuing administration of any antibiotic increases the possibility of adverse reactions but, in the majority of surgical procedures, does not reduce the incidence of subsequent infection. However, in patients undergoing prosthetic arthroplasty, it is recommended that MEFOXIN be continued for 72 hours after the surgical procedure. If there are signs of infection, specimens for culture should be obtained for identification of the causative organism so appropriate treatment may be instituted.
Contraindications: Previous hypersensitivity to cefoxitin and the cephalosporin group of antibiotics.
Warnings: BEFORE THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOXITIN, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. GIVE WITH CAUTION TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFOXITIN OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.
Pseudomembranous colitis, from mild to life-threatening in severity, has been reported with virtually all antibiotics (including cephalosporins); therefore, it is important to consider its diagnosis when diarrhea develops in association with antibiotic use. Broad-spectrum antibiotics alter normal flora of colon and may permit overgrowth of clostridia; a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated colitis. Mild cases may respond to drug discontinuance alone; in more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte and protein supplementation, and use of a drug such as oral vancomycin; isolation of the patient may be advisable. Other causes of colitis should also be considered.
Precautions: *General*—Total daily dose should be reduced in patients with reduced urinary output d
renal insufficiency because high and prolonged serum antibiotic concentrations can occur from usual d
Prescribe with caution in patients with a history of gastrointestinal disease, particularly colitis. Prolo
use may result in overgrowth of nonsusceptible organisms; repeated evaluation of the patient's conditi
essential. If superinfection occurs, take appropriate measures.
Drug Interactions—Increased nephrotoxicity has been reported following concomitant administrati
cephalosporins and aminoglycoside antibiotics.
Drug/Laboratory Test Interactions—High concentrations (>100 mcg/mL) may interfere with measureme
serum and urine creatinine levels by the Jaffé reaction and produce false increases of modest degr
creatinine levels reported; serum samples should not be analyzed for creatinine if withdrawn within 2 h
of cefoxitin administration. High concentrations may interfere with measurement of urinary 17-hydr
corticosteroids by the Porter-Silber reaction and produce false increases of modest degree in l
reported. A false-positive reaction for glucose in urine has been observed with CLINITEST** reagent tab
Carcinogenesis, Mutagenesis, Fertility Impairment—No long-term animal study has been performe
carcinogenic or mutagenic potential. Rat studies at approximately three times maximum recomme
human dosage revealed no effects on fertility or mating ability.
Pregnancy Category B—Reproduction studies in rats and mice did not reveal teratogenic or fetal
effects, although fetal weights were slightly decreased. In rabbits, cefoxitin was associated with a
incidence of abortion and maternal death, neither considered teratogenic. There are, however, no adec
and well-controlled studies in pregnant women. Because animal reproduction studies are not al
predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers—Excreted in human milk: Exercise caution.
Pediatric Use—Safety and efficacy in infants from birth to three months have not yet been establishe
children three months and older, higher doses have been associated with increased incidence of eosino
and elevated SGOT.
Adverse Reactions: The most common adverse reactions have been local reactions following intrave
or intramuscular injection. Other adverse reactions have been encountered infrequently. *Local Reacti*
Thrombophlebitis with intravenous administration; pain, induration, and tenderness after intramus
injections. *Allergic Reactions*—Rash (including exfoliative dermatitis), pruritus, eosinophilia, fever, and
allergic reactions including anaphylaxis. *Cardiovascular*—Hypotension. *Gastrointestinal*—Diarrhea, in
ing documented pseudomembranous colitis during or after treatment, and, rarely, nausea and vomi
Blood—Eosinophilia, leukopenia including granulocytopenia, neutropenia, anemia, including hem
anemia, thrombocytopenia, and bone marrow depression. A positive direct Coombs test may devel
some individuals, especially those with azotemia. *Liver Function*—Transient elevations in SGOT, SGPT, s
LDH, and serum alkaline phosphatase; jaundice. *Renal Function*—Elevations in serum creatinine a
blood urea nitrogen levels and, rarely, acute renal failure.
Note: In group A beta-hemolytic streptococcal infections, therapy should be maintained for at least 10
to guard against the risk of rheumatic fever or glomerulonephritis. In staphylococcal and other infec
involving a collection of pus, surgical drainage should be carried out where indicated. Intramus
injections should be well within the body of a relatively large muscle such as the upper outer quadrant
buttock (i.e., gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel
total daily dosage in infants and children should not exceed 12 grams.
How Supplied: Sterile cefoxitin sodium in vials, infusion bottles, and ADD-Vantage®† vials contai
1 gram or 2 grams cefoxitin equivalent and in 10-gram bulk bottles.

B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus

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Novel Therapy for the Treatment of Human Carcinoid

B. MARK EVERS, M.D.,* STEPHEN C. HURLBUT, M.D.,* STEPHEN K. TYRING, M.D., PH.D.,†
COURTNEY M. TOWNSEND, JR., M.D.,* TATSUO UCHIDA, B.S.,‡ and JAMES C. THOMPSON, M.D.*

Development of effective treatment for patients with carcinoid tumors has been hampered by lack of an experimental model. The authors have established the only long-term cell line of a functioning human pancreatic carcinoid tumor (BON) that produces tumors in nude mice. In this study the authors examined the effect of three agents, α-interferon (IFN), a somatostatin analog, SMS 201-995 (SMS), and an inhibitor of polyamine biosynthesis, α-difluoromethylornithine (DFMO), on the growth of BON tumors. BON was implanted bilaterally as 3-mm^2 pieces (subcutaneously [sc]) into male BALB/c nude mice. In the first study, 23 mice were randomized to four groups: control, IFN (1×10^6 units, sc, four times a day), IFN + SMS (300 μg/kg, intraperitoneally, three times a day), and IFN + 3% DFMO in drinking water. Treatments were initiated on day of tumor implantation. In the second study, mice were randomized to six groups: control, IFN, SMS, DFMO, IFN + SMS, IFN + DFMO, and IFN + SMS + DFMO. Treatments were started on day 15 after tumor implantation. Tumor area and body weights were measured weekly. In both studies mice were killed on day 28 after BON implantation and tumors removed, weighed, and analyzed for DNA and RNA content. In the first study, IFN either alone or in combination with SMS or DFMO suppressed BON tumor growth. When treatment was initiated after established tumor growth (study 2), however, the only effective treatments for suppression of growth of BON were IFN + DFMO and IFN + DFMO + SMS. It is concluded that combinations of these agents may offer an effective and relatively nontoxic approach for treatment of carcinoid tumors. This unique tumor will provide an excellent model to study effects of various treatment strategies.

From the Departments of Surgery, Dermatology,† and the Office of Academic Computing and Biostatistics,‡ The University of Texas Medical Branch, Galveston, Texas*

DEVELOPMENT OF AN effective chemotherapeutic strategy for carcinoid tumors of the gut has been hampered by the relative rarity of the disease and lack of an *in vivo* model to evaluate tumor inhibition. In the past the treatment of carcinoid tumors of the gut has largely been directed toward symptomatic relief of the devastating sequelae of the carcinoid syndrome.[1-6] Combinations of various chemotherapeutic agents, evaluated in limited clinical trials, have been ineffective in slowing the growth of these tumors, and, in addition, treatment with these toxic agents is fraught with numerous debilitating side effects.[1,7-9]

We have been interested for years in the experimental investigation and development of novel and nontoxic agents for the treatment of gastrointestinal (GI) cancers. We have demonstrated that somatostatin, a peptide that blocks the release of growth hormone and all known GI hormones, and α-difluoromethylornithine (DFMO), an inhibitor of polyamine biosynthesis, can inhibit growth of animal and human gut cancers.[10-14] Recently we have shown that the long-acting somatostatin analog, SMS 201-995 (SMS), and DFMO suppress the growth of human pancreatic carcinoid (BON) xenografts in nude mice.[15]

Interferon-α (IFN) is a naturally occurring protein produced by leukocytes in response to viral infections.[16] Administration of large doses of IFN has been shown to inhibit growth of a wide range of cancers.[17-21] Recent studies have suggested that administration of IFN can suppress the growth of carcinoid tumors and ameliorate symptoms associated with carcinoid syndrome.[22-26] In addition, IFN alone appears to be less toxic and more effective in producing subjective relief of symptoms and tumor inhibition than the combination of streptozocin and 5-fluorouracil (5-FU).[27]

The purpose of the present study was to evaluate the effect of IFN, either alone or in combination with SMS or DFMO, on the growth of BON, a human pancreatic

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carcinoid tumor that has been xenografted into nude mice. In the second part of this study, we evaluated these agents alone or in various combinations in the treatment of established BON tumor.

Materials and Methods

Human Carcinoid Tumor Line

A specimen of a metastatic carcinoid tumor of the pancreas was obtained 5 years ago from a 28-year-old man at the time of exploratory laparotomy. We successfully established a cell line, which we call BON, in tissue culture. BON is currently maintained in Dulbecco's modified Eagle's medium (DMEM) (Gibco, Grand Island, NY) and F12K (Gibco) in a 1:1 ratio supplemented with 10% (vol/vol) fetal calf serum (FCS) (Hyclone Laboratories, Logan, UT); it is passed at a 1:2 ratio when cells reach 80% confluence. Cell cultures are monitored routinely for mycoplasma contamination using a fluorescent stain (Hoeschst #33258), and no mycoplasma growth has been detected. BON has retained its original histologic appearance, which is that of a poorly differentiated neuroendocrine tumor. BON cells possess gastrin and somatostatin receptors and synthesize serotonin and chromogranin A. Single-cell suspensions (1×10^7 cells) of BON cells will reliably produce discrete encapsulated tumors when injected subcutaneously into athymic nude mice.

Animals

Male athymic nude mice (BALB/c, 20 to 25 g, 3 to 4 weeks of age, Life Science, St. Petersburg, FL) were housed under pathogen-free conditions in a temperature-controlled isolation unit with 12-hour light and dark cycles in accordance with the National Research Council's Guide for the Care and Use of the Nude Mouse in Biomedical Research.[28] The mice were fed a standard chow (Autoclavable Rodent Chow #5010, Ralston Purina, St. Louis, MO) and sterile water, both given *ad libitum.*

Experimental Design

In both experiments, dispersed BON cells (passage 8) from tissue culture were inoculated subcutaneously (sc) in four to eight nude mice (1×10^7 cells/injection) to establish tumors. When tumors became approximately 10 cm^2 in area, the mice were killed and tumors minced into 3-mm^2 pieces, which were then implanted bilaterally into the flanks of nude mice.

In the first experiment, 23 mice were randomly allocated to receive either saline (0.1 mL, intraperitoneally [ip], three times a day, and 0.1 mL, sc, every morning), IFN (recombinant interferon-α-2a, 1×10^6 units, sc, every morning) alone or in combination with SMS (300 μg/kg, ip, three times a day), or 3% (wt/vol) DFMO (a gift from W. J. Hudak, Ph.D., Manager of Research Information at the Merrell Research Center, Cincinnati, OH) in drinking water. Dosages for SMS and DFMO were determined from previous studies.[13-15] The dosage of IFN was determined from a pilot study that showed this to be the maximally effective and nontoxic dose (data not shown). All treatments were started on the day of tumor implantation and continued until killing. Water bottles were covered to prevent light degradation. Drinking water was renewed every 2 days. SMS, a gift of Sandoz Research Institute, Hanover, NJ, and IFN, a gift of Hoffman La Roche Laboratories, Nutley, NJ, were diluted to the required concentration with saline.

The mice were weighed weekly; the tumors were measured twice weekly by the same observer with Vernier calipers (Mitutoyo Corporation, Tokyo, Japan) that were accurate to 0.5 mm. Surface areas of the tumors were calculated as the product of the two greatest perpendicular tumor diameters, and were expressed in square millimeters. Mice were killed on day 28 by cervical dislocation, and tumors were removed, weighed, and frozen at −70 C until assayed for DNA and RNA content.

In the second experiment, BON tumor chunks were implanted bilaterally into the flanks of 40 athymic nude mice. On day 14, all mice were weighed and tumors measured. The mice were then randomized to seven treatment groups: control (saline, 0.1 mL, ip, three times a day, and 0.1 mL sc, every morning), IFN (1×10^6 units, sc, every morning), SMS (300 μg/kg, ip, three times a day), 3% DFMO, IFN + SMS, IFN + 3% DFMO, or the combination of all three agents. Treatment was started on day 15 and continued until killing. Body weights and tumor areas were measured twice weekly. Mice were killed on day 28 after tumor implantation. Tumors were removed, weighed, and frozen at −70 C until analysis.

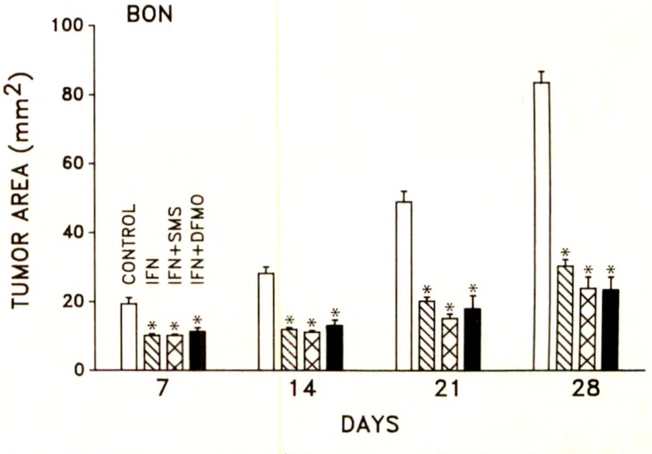

FIG. 1. BON tumor area (mm^2) in relation to time from implantation comparing interferon-α (FN) (1×10^6 units, sc, every morning; single-hatched bars, n = 12 tumors), IFN + SMS 201-995 (300 μg/kg, ip, tid; double-hatched bars, n = 12 tumors); and the combination of IFN + 3% DFMO (closed bars, n = 10 tumors) to control group (open bars, n = 12 tumors). (* = $p < 0.05$ *versus* control, one-way ANOVA).

DNA and RNA Analysis

Tumors were thawed, homogenized, extracted, and analyzed for DNA and RNA by methods that we have previously described.[29]

Statistical Analysis

Results are expressed as the mean ± standard error of the mean and were analyzed using one-way analysis of variance (ANOVA) at the 0.05 level of significance. Mean values were separated using Fisher's least significant difference procedure.

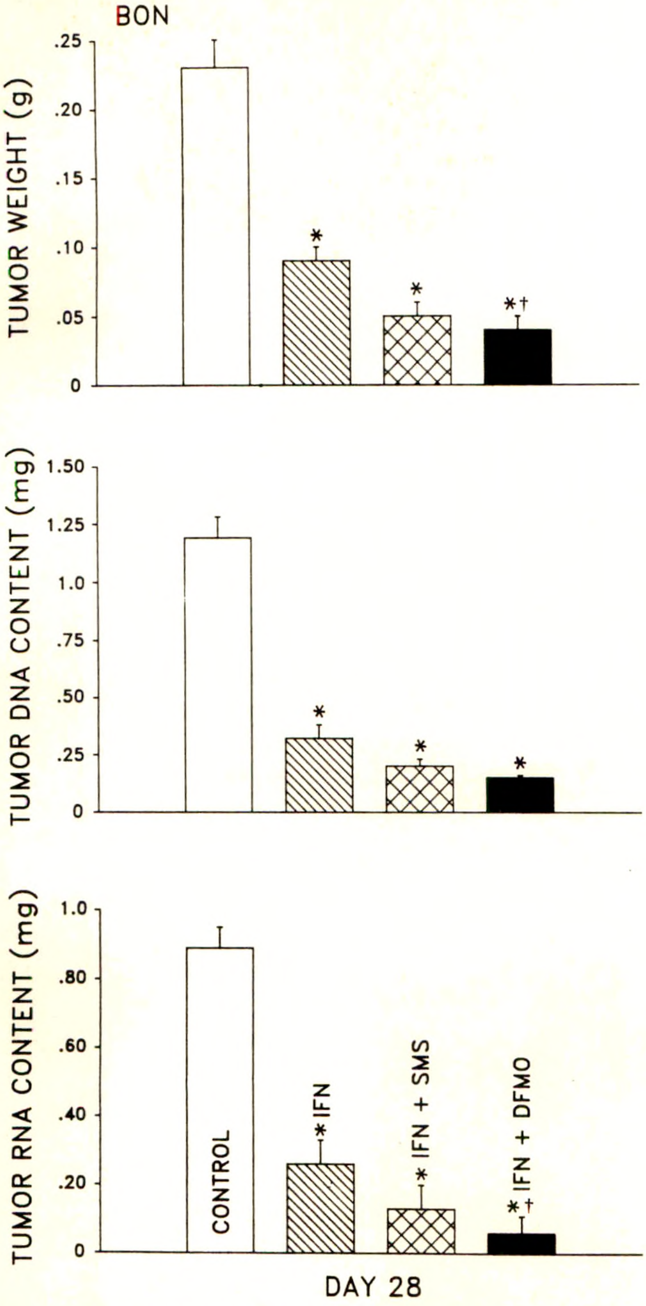

FIG. 2. Tumor weight (g), DNA and RNA content (mg) of BON tumors in control group (open bars, n = 12), IFN group (single-hatched bars, n = 12), IFN + SMS 201-995 (double-hatched bars, n = 12), IFN + DFMO (closed bars, n = 10) when killed (* = $p < 0.05$ *versus* control; + = $p < 0.05$ *versus* IFN; one-way ANOVA).

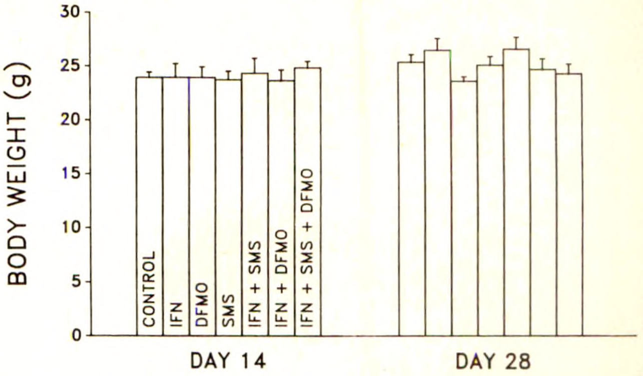

FIG. 3. Body weights (g) of mice at time of initiation of treatment (day 14) and final body weights when killed (day 28).

Results

Experiment 1

There were no significant differences in final body weight in treated mice compared with the control group. Food and water intake were monitored and there were no differences in consumption between groups (data not shown).

Figure 1 demonstrates BON tumor progression in square millimeters over the 28-day treatment period. IFN, administered alone or in combination with either SMS or DFMO, significantly inhibited tumor area by day 7; inhibition continued to the time of killing (day 28). Tumors treated with IFN + DFMO were significantly smaller than those treated with IFN alone. Tumor weight, DNA, and RNA contents are shown in Figure 2. The mean tumor weight of the IFN-treated group was 63% of that of the control group; DNA content was 73% and RNA content 71% of controls. Combining SMS with IFN produced no further decreases in tumor values compared with IFN alone; however, the combination of IFN + DFMO was statistically more effective in suppressing tumor weight and RNA content.

Experiment 2

Body weights of mice were similar at the time treatment was begun, and there were no differences in final body weights at time of killing (Fig. 3).

Tumor areas were similar in all groups before initiating treatment (Fig. 4). After 2 weeks of treatment, only 3% DFMO, as a single agent, was effective in inhibiting final tumor area. Inhibition of BON tumor area by IFN + DFMO and the combination of all three agents was similar to that of DFMO alone (Fig. 4).

Tumor weights and DNA content are shown in Figure

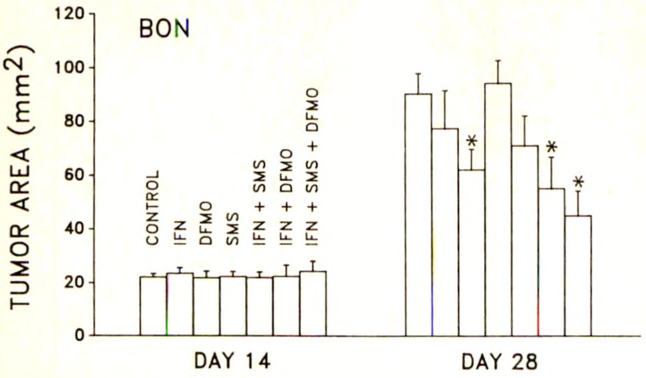

FIG. 4. BON tumor area (mm^2) at time of initiation of treatment (day 14) and final tumor area after 2 weeks treatment (day 28).

5. Similar to results of tumor area, neither IFN nor SMS were effective in suppressing tumor weight or DNA when administered as single agents. Although tumor area was suppressed by DFMO alone, weight and DNA content were not affected. IFN + DFMO and the combination of all three agents significantly inhibited BON weight and DNA content. Analysis of the seven groups by ANOVA demonstrated no significant differences in tumor RNA content ($p = 0.08$); however the same general trend in mean values exists as noted with area, weight, and DNA, even though statistical significance was not obtained (Table 1).

Discussion

The human pancreatic carcinoid cell line, BON, grows as discrete masses when injected subcutaneously into athymic nude mice, thus providing a unique opportunity to evaluate *in vivo* effects of various chemotherapeutic agents on the growth of a functioning human foregut carcinoid tumor.

Recently several clinical studies have evaluated the effect of IFN on the growth and symptomatic relief in patients with carcinoid tumors.[22–26] Significant subjective improvement in symptoms associated with decreases in 5-HIAA levels was reported, with median duration of response varying from 6 to 34 months. Tumor size remained stable or actually decreased in 40% to 80% of patients in these series. In addition, in a randomized controlled study of IFN compared with combination treatment of streptozocin and 5-FU, IFN treatment was judged superior based on a significantly higher proportion of patients who demonstrated stable disease and less side effects. Other reports of IFN therapy for carcinoid tumors have been less encouraging. Initial good results were short-lived in a series by Moertel and colleagues,[30] who noted subjective improvement in 65% of patients and a decrease in tumor size in 20%; however, the median duration of response was only 7 weeks. In our present study, IFN, administered as a single agent, inhibited growth of BON when treatment was initiated at time of tumor placement; however, when treatment was begun after established tumor growth, no significant inhibitory effects were noted.

We[31] recently reviewed the effects of somatostatin on growth of both solid and endocrine cancers. Antitumor effects of somatostatin appear to be mediated both by a direct action by specific somatostatin receptors and by an indirect effect by decreasing secretion of gut hormones and other growth factors. In contrast the action of DFMO is quite specific. α-Difluoromethylornithine blocks production of polyamines by inhibiting ornithine decarboxylase, the rate-limiting enzyme in polyamine biosynthesis.[32] Polyamines are the building blocks of proteins and are essential for rapidly dividing tissues. We have previously shown that the long-acting somatostatin analog, SMS, and DFMO were equally effective in inhibiting BON tumor growth when administered at time of tumor placement.[15] In the present study, only DFMO was effective as single-agent therapy in suppressing area of established BON tumors. Tumor weight, DNA, and RNA contents were not suppressed with any of the agents administered alone. From these results, it appears that these agents, at the doses administered, are not effective as single-agent therapy in suppressing established tumor growth.

The combination of chemotherapeutic agents that block tumor growth at different steps in the cell cycle are more effective than single-agent therapy. Similarly, in our pres-

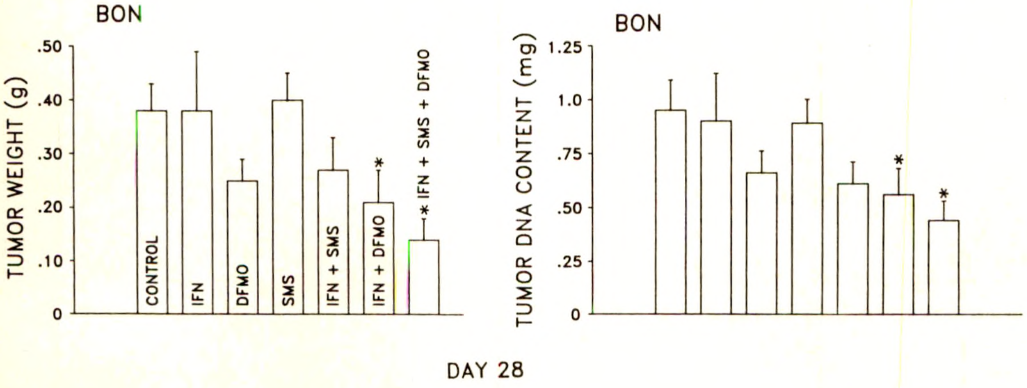

FIG. 5. BON tumor weight (g) and DNA content (mg) comparing interferon-α (IFN) (1×10^6 units, sc, every morning), SMS 201-995 (300 μg/kg, ip, tid), 3% DFMO, IFN + SMS, IFN + DFMO, and IFN + SMS + DFMO. ($n = 10$ to 12 tumors/group; * = $p < 0.05$ *versus* control, one-way ANOVA).

TABLE 1. *Effect of Therapy on BON Tumor RNA Content*

	Tumor RNA Content (mg)
Control	2.0 ± 0.3
IFN	2.1 ± 0.6
DFMO	1.5 ± 0.3
SMS	2.3 ± 0.3
IFN + SMS	1.5 ± 0.3
IFN + DFMO	1.4 ± 0.3
IFN + SMS + DFMO	0.9 ± 0.2

Values indicate the mean ± SEM (n = 10 to 12 tumors/group).

ent study, various combinations were found to be more effective in suppressing BON growth; however, unlike traditional chemotherapeutic regimens, there was not an associated increase in morbidity rate. Combining IFN with DFMO inhibited BON tumor weight and RNA content more than IFN alone when treatment was started at time of tumor implantation. The combination of IFN + DFMO and IFN + DFMO + SMS suppressed established BON tumor growth when compared with controls in the second study. Mean values of area, weight, and DNA content were decreased in those tumors treated with all three agents; however these did not represent significant differences compared with DFMO alone or IFN + SMS or DFMO. It is possible that a longer treatment period would have demonstrated a greater tumor suppression after administration of all three agents.

The molecular mechanisms responsible for the antitumor effect of IFN are not completely understood. α-Interferon induces a specific protein kinase that phosphorylates eukaryotic-initiation-factor 2 (eIF-2), which prevents subsequent translation[33,34] and, therefore, suppresses protein synthesis. An additional possible mechanism of IFN action could be a reduction of c-*myc* mRNA levels, which has been noted in correlation with a cessation of growth after IFN treatment; however these findings appear tissue specific and do not occur in all circumstances.[35]

The mechanism underlying the enhanced suppression of BON tumor with interferon in combination with DFMO is not clear. Sunkara and colleagues[36] noted a similar effect of IFN combined with DFMO in treating a melanoma cell line and a human lung cancer line. In their study, polyamine levels were decreased after DFMO but not IFN. We could postulate that tumor inhibition is attained at multiple levels (*e.g.*, inhibition of polyamine biosynthesis, protein translation, and oncogenes associated with cell growth), and, therefore, this therapy is more effective because of a block in multiple pathways necessary for cell growth.

In conclusion we found that IFN alone suppresses BON tumor growth when started at the time of initial tumor placement; however, there was no effect on established tumor growth when given alone. Combination of IFN with DFMO or IFN + DFMO + SMS produced significant suppression of established tumor growth without an associated increase in toxicity. Therapeutic use of these agents in combination may offer an effective and relatively nontoxic alternative in the treatment of carcinoid tumors. The tumor line BON should prove to be a useful model to determine the most effective treatment schedules and dosages.

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DISCUSSION

DR. JOHN MCDONALD (Shreveport, Louisiana): It is not surprising that a somatostatin analogue and/or an inhibitor of polyamine synthesis will inhibit the implantation of tumor. There are data from others that suggest that growth factors and polyamine are required for metastases to become established. And I suppose the implantation of these tumor cells is more akin to the metastatic process than to *de novo* tumor growth, which probably explains why there was a less impressive effect on established tumor growth in their second experiment.

The effect of interferon is more perplexing, because, to my knowledge, the known pathways of interferon action involve primarily its effect on thymic-derived lymphocytes, of which the nude mice has none.

I would ask the investigators how they envision interferon producing its effect in this model. Second the paper suggests that this may be a means of treating carcinoid tumor. What evidence have we to believe that these cells, passed in culture many times and implanted into an immunologically incompetent animal, behave in any way like the original tumor? For example, does it metastasize? Does it grow to kill the animal, and so forth?

Finally will these agents affect other cell lines of human tumor or some of the many established animal tumors available for study? In other words, how specific or general is the effect produced here?

The concept of developing tumor treatment with nontoxic biologic agents seems to me to be very important, and these studies are encouraging steps in that direction.

DR. MARSHALL URIST (Birmingham, Alabama): The authors appear to have developed a very challenging model that, in many ways, repeats the properties of the naturally occurring tumor.

In the experiments that they have shown, treating the tumors at the time of implantation has been effective; however when established tumors are present, the challenge is much greater.

I, therefore, would like to ask what happens when treatment is continued beyond 2 weeks in those animals that have therapy established after the tumor has begun to grow? Are there any circumstances under which actual tumor regression can be observed?

The use of these agents in human trials initially appears to be rewarding; however in further trials the high response rates are found to be brief and, in fact, there has been no demonstration that treatment with these particular agents has any effect on overall patient survival.

Because these are functioning tumors, is there any evidence that the use of these different agents does, in fact, inhibit the proliferation of these different compounds from the tumors?

What is the mechanism of action in this situation, especially the combination of all three agents?

DR. PAUL JORDAN (Houston, Texas): I just wondered, Dr. Townsend, what the definition for a carcinoid was. I think you gave us that in the beginning, but I wonder—where does the microcarcinoidosis of the stomach that we are hearing about now fit? That is supposed to come from an ECL-like cell. Is it a different kind of carcinoid? Do you expect this method of treatment to work for all carcinoids, regardless of what hormone the tumor makes?

DR. MARK EVERS (Closing discussion): Dr. McDonald asked about the mechanism of action of α-interferon in our model. Specifically was this a direct antitumor effect or were the effects indirect as a result of enhancing the immunologic system? We believe that the effects of interferon were directly mediated. Studies have shown that α-interferon can directly inhibit protein synthesis at either the transcriptional or translational level. In addition we have treated BON cells *in vitro* with α-interferon and have noted a similar, dose-related inhibition of tumor growth.

The second question was regarding the characteristics of our tumor line compared with the original patient tumor. For all of our studies, we use BON cells in early passage (that is passages 8 to 12). Histologically, these tumors are identical to the original tumor. In addition, they produce serotonin, pancreastatin, neurotensin and chromogranin A as was noted from the original operative specimen. The BON tumors in nude mice grow as discrete tumors and do not metastasize.

The last question was whether we have examined the effect of somatostatin or DFMO on the growth of other tumors. Our laboratory has worked extensively with both agents and have found a wide range of inhibitory effects on pancreatic, stomach, and colon cancers.

Dr. Urist asked whether these agents decrease either the synthesis or release of secretory products. We have not studied the effects of either DFMO or α-interferon on secretion; however we have studied the effects of somatostatin and found a decrease in both the synthesis and release of serotonin.

Finally Dr. Jordan asked whether gastric carcinoid tumors arise from the same cell type. To our knowledge, carcinoid tumors have been described in almost every organ in the body and all arise from Kulschitzsky cells.

Ruptured Aneurysm of the Descending Thoracic and Thoracoabdominal Aorta

Analysis According to Size and Treatment

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Acute rupture was confirmed at operation in 117 patients treated for descending thoracic or thoracoabdominal aortic aneurysm. Descending thoracic (n = 80) aortic rupture occurred into lung or esophagus in 8, the pleural cavity in 49, and the mediastinum in 23. Upper abdominal aortic (n = 37) rupture occurred into peritoneal cavity in 3 and into retroperitoneal tissues in 34. Aneurysmal size (range, 5 to 17 cm; median, 8 cm) could be determined retrospectively in 86 patients; 59 (74%) descending thoracic and 27 (73%) abdominal aorta. Size (external diameter) in the former was 8 (14%), 5 to 6 cm; 21 (36%), 6 to 8 cm; 23 (39%), 8 to 10 cm; and 7 (12%) > 10 cm. Size at the abdominal site was similar. Thus size was not greater than 10 cm in 52 (88%) (range, 5 to 10 cm), which contradicts opinions that thoracic aneurysms rupture only when size exceeds 10 cm. Twenty-nine patients (25%) were hypotensive (systolic blood pressure less than 100 mmHg), of whom 16 (55%) had cardiac arrest before operation. Associated conditions included advanced age (≥75 years) in 26 (22%), coronary artery disease in 41 (35%), chronic obstructive pulmonary disease in 46 (39%), renal insufficiency in 25 (21%), and cardiovascular disease in 22 (18%). The overall early survival rate (30-day) was 89 of 117 patients (76%); 69% in patients with hypotension, 56% of patients with cardiac arrest, 88% in good-risk patients. Five-year (Kaplan–Meier) survival was 28%. Because elective operation is associated with 92% survival, this should be considered before rupture when aneurysm is 5 cm or larger in good-risk patients, in patients with symptomatic aneurysms, and in most patients with larger aneurysms.

ANEURYSMS OF THE descending thoracic and thoracoabdominal aorta may be associated with a variety of complications; however the most serious is rupture because it leads to death in most cases. Natural history studies of patients with untreated aneurysms of the thoracic aorta suggest 5-year survival varying from 7% to 20%, depending on cause; dissection, 7%; and nondissection, 20%.[1-3] Similar studies of patients with thoracoabdominal aortic aneurysms indicate less than 20% survived for 5 years.[4] To be sure, the cause of death in many of these patients was associated disease, but the most common cause, occurring in more than one half, was rupture of the aneurysm.

Rupture of ascending aortic and abdominal aortic aneurysms has been related to size in several studies.[5,6] It has been reported that rupture from laceration (simple bursting of aortic wall) or dissection occurs with increasing frequency in patients with aneurysms of the ascending aorta as the diameter increases beyond 5 cm.[5] Studies indicate that most aneurysms of the abdominal aorta are 5 cm or greater in diameter at the time of rupture.[6] Based on one follow-up study of descending thoracic aortic aneurysms in which rupture occurred in 10 patients, and the aneurysm in only one patient was less than 10 cm in diameter, the conclusion made was that rupture of descending thoracic aortic aneurysms rarely occurs in patients with aneurysms less than 10 cm in diameter.[7] Thus the opinion expressed by some authors is that aneurysms of the descending thoracic aorta that are less than 10 cm in diameter should be treated conservatively and that operative treatment should be reserved only for those with aneurysms greater than 10 cm in diameter.[8,9]

Our observations in the treatment of patients with rupture of the aortic segment of aneurysms of the descending thoracic and thoracoabdominal aorta suggested that rupture occurred in smaller aneurysms and that operation should be considered in patients with aneurysms whose diameters are less than 10 cm. This report is concerned with a retrospective review of 117 patients treated for acute rupture of the descending thoracic and thoracoabdominal

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aorta and an analysis according to size, treatment, and results in these cases as compared with those who had operation for aneurysms that had not ruptured.

Methods

Acute aortic rupture for purposes of this study was defined as loss of continuity of aortic wall in the region of aneurysm associated with fresh blood outside the wall of the aneurysm. The charts and roentgenographic records of all patients with aneurysms of the descending thoracic aorta (n = 726) treated between May 1962 and June 1, 1990 and all patients (n = 1400) with thoracoabdominal aortic aneurysms treated between June 20, 1960 and June 1, 1990 were reviewed retrospectively. Acute rupture, as defined, was found in 40 (5.5%) of the former and 77 (5.5%) of the latter patients. Of these 117 patients, 73 (62%) were men and 44 (38%) were women. Their ages ranged from 16 to 87 years with a median age of 69 years. The women tended to be older, with a median age of 71 years compared to 67 years for men.

Pertinent data relating to possible preoperative risk factors, intraoperative variables, and postoperative results were recorded and stored on computer for analysis.

Statistical Methods

Standard methods incorporating the BMDP statistical software package (BMDP Statistical Software Incorporated, Los Angeles, CA) were used. Univariate (Pearson chi square test, BMDP4F) and multivariate (stepwise logistic regression, BMDPLR) analyses were used to identify statistically significant clinical predictors of early death. The chi square test determines whether a statistically significant association exists between early death and an individual study factor (ignoring other factors). Stepwise logistic regression selects from the study factors a set of independent risk factors that demonstrated a simultaneous significant association with early mortality. The Kaplan–Meier technique was used to estimate long-term survival, and confidence intervals were computed to indicate the relative precision of the estimates. Factors studied include: preoperative cardiac arrest, preoperative hypotension, type of rupture (contained or free), location of rupture (lung/esophagus, thorax, abdomen), interval from aneurysm diagnosis to aneurysm rupture, interval from acute symptoms to operation, size of aneurysm, sex, age, presence of hypertension, chronic obstructive pulmonary disease (COPD), atherosclerotic heart disease, preoperative renal dysfunction, cerebrovascular disease, diabetes mellitus, concurrent aortic aneurysm or previous repair, Marfan's syndrome, aortic dissection, fever, pleural effusion, emergency nature of operation, pump-bypass use, period of operation, extent replaced, aortic cross-clamp time, pulmonary complications, stroke complications, cardiac complications, reoperation for postoperative bleeding, wound complications, vocal cord paralysis, hemodialysis, and neuromuscular dysfunction. Thus a total of 33 factors were studied: 20 preoperative, 5 intraoperative, and 8 postoperative. Because of the *post hoc* nature of the statistical analysis, the large number of significant tests performed, and the small number of patients involved in some of the comparisons, the reported p values should be interpreted with caution.

TABLE 1. *Interval Between Diagnosis of Aneurysm and Onset of Symptoms (108 Patients with Data)*

Interval	No. of Patients
1–6 days	33 (31%)
7–29 days	19 (18%)
1 month–2 years	30 (28%)
2–10 years	26 (24%)

TABLE 2. *Interval Between Change in Symptoms and Operation (114 Patients)*

Interval	No. of Patients
<24 hours	18 (16%)
1 day	17 (15%)
2 days	18 (16%)
3–6 days	22 (19%)
7–14 days	24 (21%)
2 weeks–4 months	15 (13%)

Pathology

The cause of aneurysm was aortic dissection in 51 (44%), acute in 11 and chronic in 40, and nondissection in 66 (56%). Those patients with rupture from aneurysms due to trauma, false aneurysms occurring after previous operations, infection, and chronic contained rupture from any cause were excluded from the study. Marfan's syndrome, occurring in the younger patients, was present in eight (7%) of the patients.

The interval between the diagnosis of aneurysm and onset or change in symptoms varied from 1 day to 10 years with a median of 30 days in the 108 patients in whom this data was available (Table 1). The interval between onset of acute symptoms, suggesting change in the nature of the aneurysm or rupture, and operation varied from 0 to 120 days (median, 3 days) in the 114 patients with available data (Table 2).

Of the 77 patients with thoracoabdominal aortic aneurysms, rupture occurred in the upper abdominal aortic segment of aneurysm in 37 and the thoracic aortic segment in 40. Thus in this series of 117 patients, rupture occurred in the thoracic aortic segment in 80 (68%) patients and the abdominal segment in 37 (32%) patients.

Rupture occurred into the lung, tracheobronchial tree, or esophagus in 8 (7%), the pleural cavity or the mediastinum in 72 (62%), or the retroperitoneum or the abdominal cavity in 37 (32%) patients. Bloody pleural fluid was present in 62 (54%) of the patients.

The size of the aneurysm at the level of rupture could be estimated by retrospective review of the preoperative studies in 86 patients (74%), 74% (59 of 80) of those with rupture in the descending thoracic aorta and in 73% (27 of 37) of those with rupture in the upper abdominal aorta. The roentgenographic studies available in these cases included aortograms in 44, computed tomography (CT) scans in 38, magnetic resonance imaging in 3, and ultrasound in 1 patient.

The aneurysm diameter at the rupture site varied from 5 cm to 17 cm (median, 8 cm) (Tables 3 through 5). The size of ruptured descending thoracic aortic aneurysms was less than 10 cm in 52 (65%) of the 80 patients with rupture at this level and in 22 (81%) of the 27 patients who had rupture in the upper abdominal segments of thoracoabdominal aortic aneurysms (Table 5). Size of ruptured aneurysms varied with cause. The median diameter of ruptured acute dissections of the descending thoracic aorta was 7 cm; chronic dissection, 8 cm; and nondissection, 9 cm. Of the 10 patients with rupture of acute dissection of the descending thoracic aorta, however, the diameter at the rupture site was 5 to 6 cm in 4 patients (40%), 6.1 to 8 cm in 4 (40%), 8.1 to 10 cm in 1 (10%), and 10.1 to 18 in 1 (10%) (Table 4). The median aneurysm diameter in abdominal ruptures for both chronic dissection and nondissection aneurysms was 8 cm (Table 5). There were no ruptured acute dissections in the abdominal aorta.

Clinical Manifestation

The aneurysm was known to be present from plain chest x-rays, aortograms, or CT scans from 1 day to 10 years before rupture in 52% of patients (Table 1). Elective operation either had been declined by the patient or had not been recommended either because of age, associated disease, or diffuse nature of the aneurysm. The present illness had been heralded by chest, back, or abdominal pain, hemoptysis, hematemesis, or cardiovascular collapse. The aneurysm in 18 patients ruptured within 10 minutes to 6 hours of admission to the hospital (for imminent repair in 4); or during the postoperative period, after a first-stage prophylactic operation to reduce the risk of aneurysm operation in 4 patients, or after a coronary artery bypass graft in 1, carotid endarterectomy in 1, aortic valve replacement (AVR) ascending aorta and transverse aortic arch replacement in 1, and abdominal aortic aneurysm replacement in 1. The aneurysms ruptured during chest entry or exposure in four patients. Rupture also occurred 1 to 8 days after hospital admission for elective repair in six other patients. The delay of elective operation for these patients was for medical treatment of lung infection, renal failure, or skin infection at the prospective incision site. The aneurysm ruptured elsewhere in 99 patients, and these patients were transferred from other hospitals. Of these, seven were hypotensive before transfer. Twenty-two additional patients became hypotensive (systolic blood pressure less than 100 mmHg) at our hospital. Of these 29 hypotensive patients, 16 developed cardiac arrest and required cardiopulmonary resuscitation at our hospital.

Lung and tracheobronchial-aortic fistula was manifested by hemoptysis or blood spitting of mild degree for periods up to several weeks, but admission or transfer to us was precipitated by massive hemoptysis. Aortic esophageal fistula, occurring in three patients, was manifested first by dysphasia, then with gradual onset of anemia and occult bleeding, then finally with massive hematemesis at the time of transfer. One patient had both aortoesophageal and aortobronchial fistula. The latter three patients have

TABLE 3. *Estimated Aortic Diameter at Site of Rupture (86 Patients with Available Data)*

Size Range (cm)	Abdomen	Thorax	Total
5.0–6.0	3 (11%)	8 (14%)	11 (13%)
6.1–8.0	13 (48%)	21 (36%)	34 (40%)
8.1–10.0	6 (22%)	23 (39%)	29 (34%)
10.1–17.0	5 (19%)	7 (12%)	12 (14%)
Total	27 (100%)	59 (100%)	86 (100%)

TABLE 4. *Thoracic Aortic Diameter at Time of Rupture According to Etiology*

	Acute Dissection	Chronic Dissection	Non-dissection
Number of patients	10	20	29
Median size	7.0	8.0	9.0
Size range (cm)			
5.0–6.0	4 (40%)	2 (10%)	2 (7%)
6.1–8.0	4 (40%)	10 (50%)	7 (24%)
8.1–10.0	1 (10%)	6 (30%)	16 (55%)
10.1–17.0	1 (10%)	2 (10%)	4 (14%)

TABLE 5. *Abdominal Aortic Diameter at Time of Rupture According to Etiology*

	Chronic Dissection	Non-dissection
Number of patients	6	21
Median size	8.0	8.0
Size range (cm)		
5.0–6.0	2 (33%)	1 (5%)
6.1–8.0	2 (33%)	11 (52%)
8.1–10.0	1 (17%)	5 (24%)
10.1–17.0	1 (17%)	4 (19%)

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been reported in detail elsewhere.[10–12] All of these patients had pain as described above. Aneurysm of the descending thoracic aorta was manifested by chest, back, or shoulder pain. Rupture in abdominal segments of thoracoabdominal aortic aneurysms was manifested by development or increase in abdominal, left flank, left shoulder, or back pain. Associated conditions included COPD in 46 (39%), history of hypertension in 91 (78%), arteriosclerotic heart disease in 41 (35%), cerebrovascular disease in 22 (19%), preoperative renal dysfunction (creatinine level more than 2 mg/dL) in 25 (21%), and diabetes in 9 (8%) patients. Either previous aortic aneurysm operations had been performed for distal aneurysms or other aneurysms were still present in 59 (50%) of the patients.

Treatment

Of the 16 patients who had cardiac arrest, three died by the time of arrival in the operating room; in other words, they had dilated fixed pupils, all reflexes had disappeared, and there were no signs at efforts of spontaneous respiration. These patients were not submitted to operation. Operation was employed in the treatment of the remaining 114 patients according to technique described in detail elsewhere.[10–13]

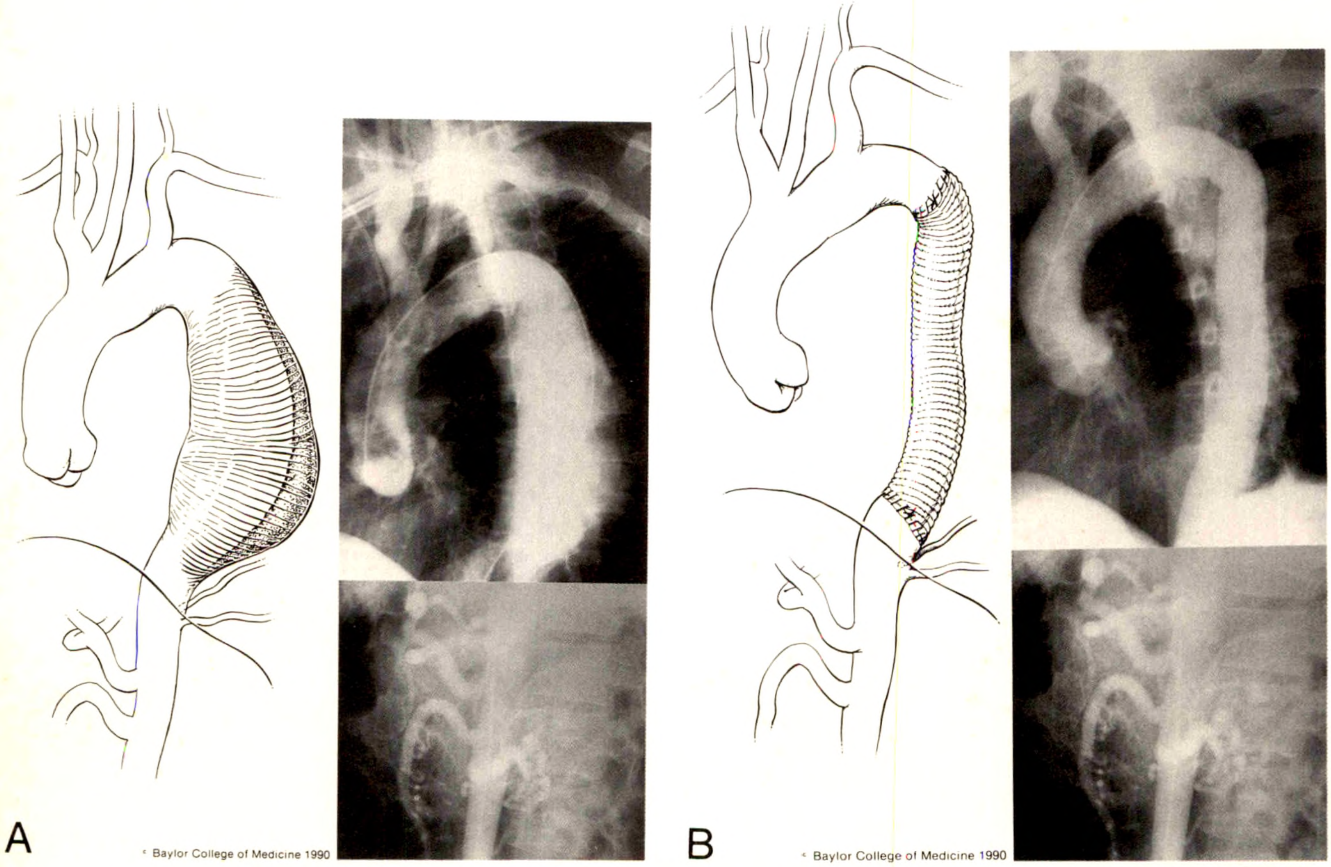
Simple proximal aortic cross-clamp was used in patients being resuscitated for cardiac arrest, in patients with severe hypotension, and in most patients with normal or stable cardiovascular hemodynamics, as illustrated by the following case report.

Case Reports

Case 1

Example of patient with hypotension and cardiopulmonary arrest treated by simple cross-clamp and blood volume resuscitation and graft replacement (Fig. 1).

A 56-year-old man with symptomatic aneurysm of the descending thoracic aorta awaiting operation in the intensive care unit developed chest pain, severe hypotension, and cardiac arrest. Cardiorespiratory resuscitation and blood transfusion were begun immediately and the patient was transferred to the operating room. The left chest was opened and the aorta exposed and clamped immediately distal to the left subclavian artery. The heart was resuscitated with massage, and blood pressure was restored to normal with blood transfusions. The aortic graft was inserted rapidly in a routine fashion with a cross-clamp time of 15 minutes and a relative cerebral ischemic time of approximately 19 minutes (time between arrest and restoration of normal brachiocephalic blood flow). This patient developed seizures and encephalopathy after operation but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FIGS. 1A and B. Illustration of a patient with rupture of a symptomatic aneurysm of the descending thoracic aorta. (A) Drawing and aortogram shows location and extent of descending thoracic aortic aneurysm. (B) Drawing and aortogram shows graft in place and functioning.

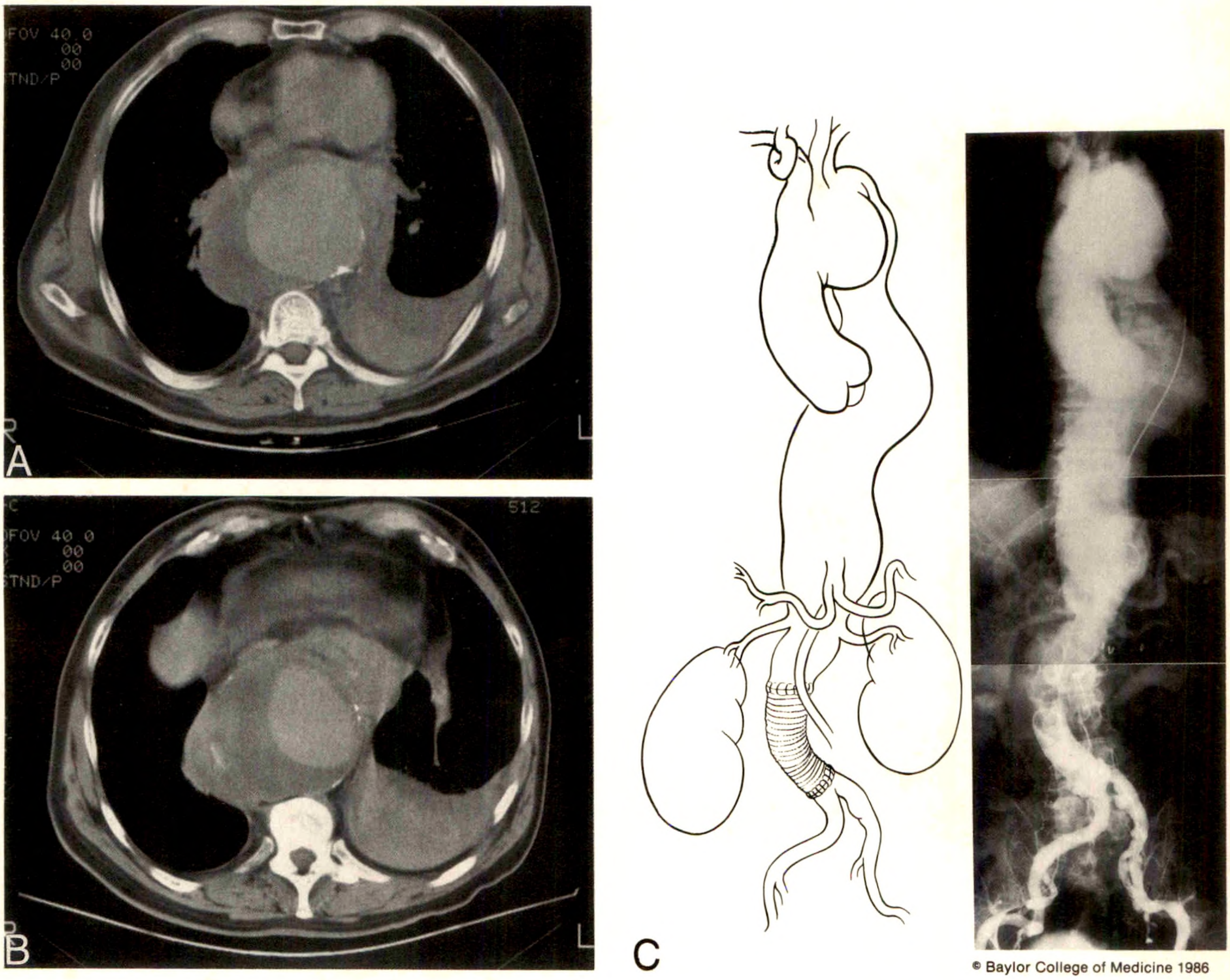
gradually recovered normal cerebral function within a period of 2 weeks. However he had persistent paresis of the lower extremities. He later had successful graft replacement of infrarenal abdominal aortic aneurysm and left nephrectomy for cancer of the kidney.

Aortoesophageal fistula was treated by *in situ* graft replacement of the aortic aneurysm combined with esophagectomy and gastroesophagostomy in one, total thoracic esophagectomy with tube gastrostomy and end cervical esophagostomy with later esophageal reconstruction by colon interposition in one, and primary esophageal repair with coverage by omental pedicle hinged on the left gastroepiploic vessels in one patient, as previously described.[10–12] Pulmonary and bronchopleural defects were treated by continuous chest tube drainage. Local and sputum cultures were obtained in the latter cases. Appropriate high-dose intravenous antibiotics were given intravenously for 1 month, then oral antibiotics were continued forever afterwards in all five cases with tracheobronchial or aortoesophageal fistulae.

Femoral vein to femoral artery cardiopulmonary bypass was employed in treatment of 23 (20%) patients who were considered possible candidates for profound hypothermia and circulatory arrest.[13] The latter technique was actually used in seven patients. The principal indications for the latter procedure in these cases were to avoid entering the aneurysm during exposure of the proximal aortic segment for clamping, to arrest the circulation to complete aortic operation in patients in whom aortic bleeding occurred during the operation, and to avoid entering the aneurysm during chest opening for the operation. The various strategies of its application are illustrated by the following brief case reports.

Case 2

Hypothermic arrest to prevent bleeding during proximal aortic exposure for clamping. A 75-year-old man who had symptomatic degenerative aneurysmal disease of the ascending aorta, transverse aortic arch, and descending thoracic and upper abdominal aorta was admitted, 5 years after graft replacement of the infrarenal abdominal aorta for aneurysm. He had chest pain but stable cardiovascular hemodynamics and normal blood pressure. Both the preoperative CT scan and observations at op-



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FIGS. 2A–F. Illustration of a patient with contained rupture of the upper descending thoracic aorta treated by graft replacement using bypass and profound hypothermic arrest without clamping. (A–B) CT scan shows left pleural fluid and blood clot surrounding the transverse aortic arch and descending thoracic aorta. (C) Drawing and aortogram made before operation showing location and extent of aneurysm disease. (D) Method of cardiopulmonary bypass using pump oxygenation, heat exchanger, and femoral artery and vein cannulation. (E) Method of aortic reconstruction. (F) Drawing and aortogram made after operation showing graft in place and functioning.

eration showed the upper mediastinum to be filled with fresh clot, and the site of proximal aortic rupture could not be determined for isolation of uninvolved proximal segment for clamping without exploration that may have caused uncontrollable hemorrhage (Fig. 2A). Cardiopulmonary bypass with femoral vein and femoral artery cannulation was instituted and the nasopharyngeal and rectal temperatures were reduced until the electroencephalogram (EEG) became silent. Cardiopulmonary bypass was discontinued and circulation arrested. Without clamping the aorta was replaced from just above the coronary artery origin to just above the renal arteries by the technique shown in Figure 2D through E.[13] Air was removed from the heart and graft, then cardiopulmonary bypass resumed, the heart restarted, and the patient rewarmed to normal temperature. He recovered uneventfully (Fig. 2F).

Case 3

Hypothermic arrest to prevent uncontrollable hemorrhage during chest opening. A 77-year-old woman who had had ascending aortic replacement for acute aortic dissection 22 years before admission and upper descending thoracic aortic replacement for chronic dissection 17 years before entry presented with lower left chest pain, left pleural effusion, a pulsating mass under the scar of the previous operation, and hypotension (Fig. 3). Computed tomography scan showed a large aneurysm of the descending thoracic aorta extending into the chest wall in the region of the last operation (Figs. 3A to C). To prevent rupture and fatal hemorrhage on opening the chest, cardiopulmonary bypass, profound hypothermia, and circulatory arrest was achieved first using the method described in case

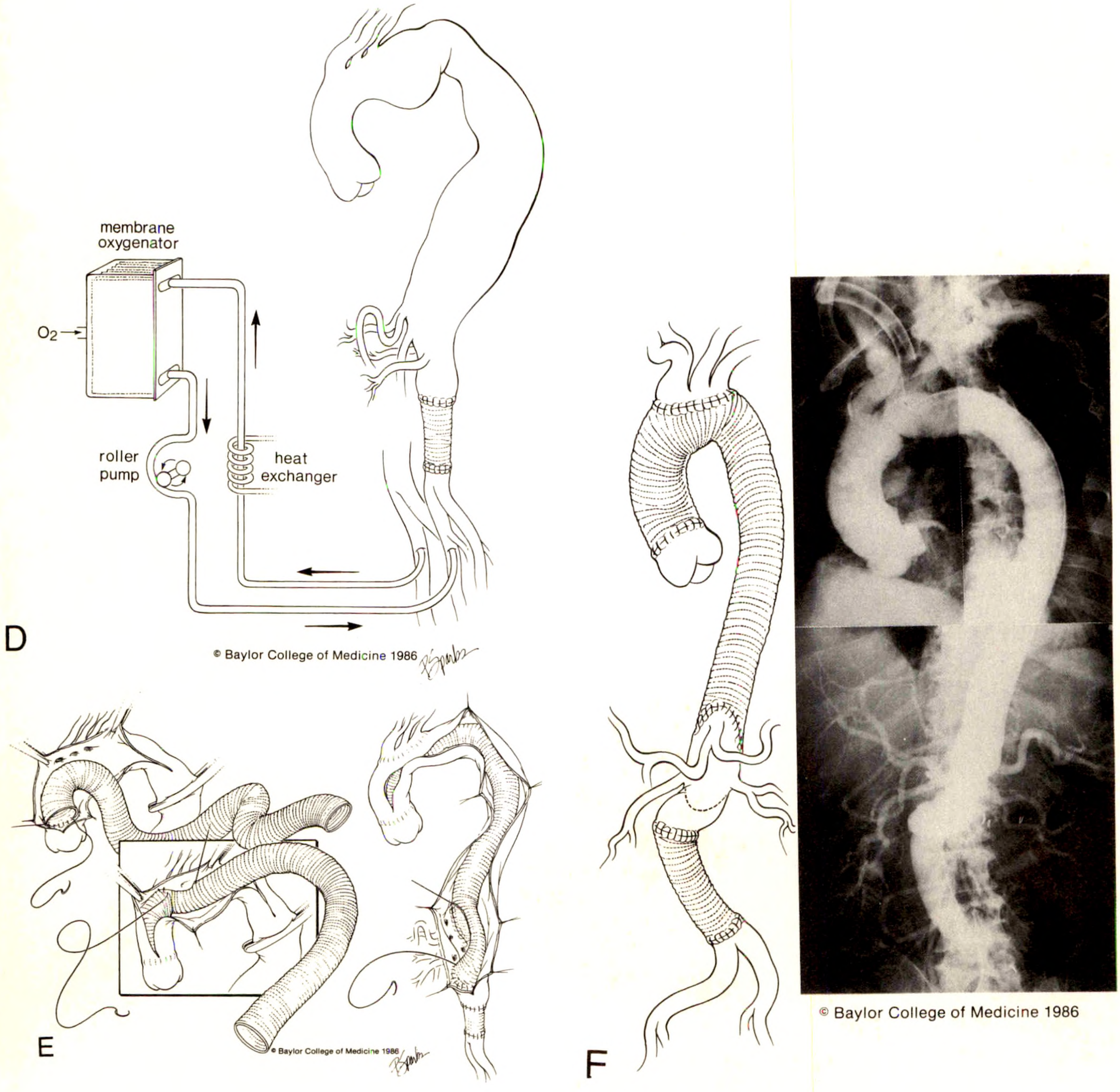

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FIG. 2. (*continued*)

2.[13] The chest was then opened and the aneurysm was successfully replaced with a Dacron tube graft. Air was evacuated, cardiopulmonary bypass restarted, and the patient rewarmed to normal temperature. She recovered from operation.

Case 4

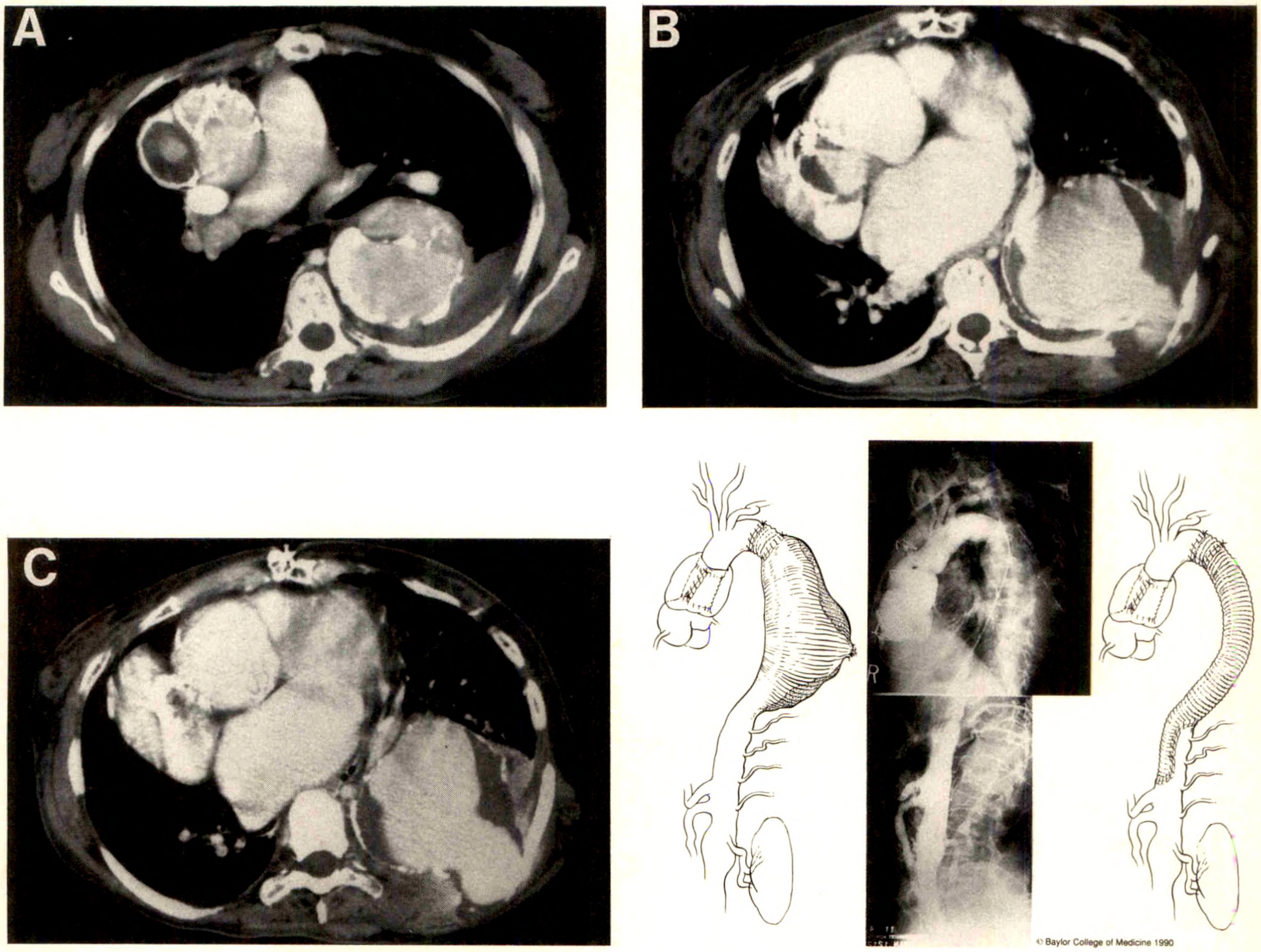
The use of hypothermic arrest in patients in whom rupture occurred during dissection and simple cross-clamping. A 60-year-old man developed bleeding in the upper descending thoracic aorta during exposure and clamping for aneurysm of the descending thoracic aorta. The clamp was removed and the bleeding was controlled by pressure. Cardiopulmonary bypass, profound hypothermia, and circulatory arrest were obtained as in cases 1 and 2. The aneurysm was replaced, without aortic clamping, circulation resumed, the patient was rewarmed and he recovered satisfactorily and later had successful replacement of a thoracoabdominal aortic aneurysm involving the lower thoracic and abdominal aorta.

Case 5

Example of a patient who had cardiopulmonary bypass, mild hypothermia, and ischemic arrest instituted after rupture. A 65-year-old man with a ruptured aneurysm of the upper descending thoracic aorta was found to have 1.5 L of fresh blood in the pleural cavity, a large hematoma in the mediastinum surrounding the transverse aortic arch and the upper descending thoracic aorta. The left lung was adherent to this mass. To avoid opening the rupture site by dissection for exposure for proximal clamping, cardiopulmonary bypass was established as above and cooling was begun. The aneurysm spontaneously ruptured into the left pleural space when the nasopharyngeal temperature was only 33 C and while the EEG was still very active. The bleeding could not be controlled by pressure and exposure for proximal clamping could not be safely obtained. The patient was allowed to exsanguinate into the left chest. The heparinized blood was aspirated into the cardiopulmonary bypass reservoir. The heart spontaneously fibrillated and arrested. The aneurysm was incised and the graft was inserted from inside the aneurysm. Air was then removed, cardiopulmonary bypass resumed, the heart resuscitated, and the body rewarmed to normal. The total period of mild hypothermic cardiac arrest and cerebral ischemia was 12 minutes. This patient recovered completely from operation.

Case 6

Example of patient who had ischemic arrest from hemorrhage and shock resuscitated by cardiopulmonary bypass and proximal perfusion



FIGS. 3A–D. Illustration of a patient with rupture of a descending thoracic aortic aneurysm that is penetrating the chest wall. (A–C). CT scans show an aneurysm of the ascending aorta and a large aneurysm of the descending thoracic aorta eroding into the left chest wall and left pleural fluid. (D) Drawing on left, aortogram in middle, and drawing on right that show location and extent of aneurysm and the extent of replacement using hypothermic arrest to prevent hemorrhage at time of chest entry.

TABLE 6. *Causes of Death (63 Patients)*

Causes	Early	Late
Cardiac	21 (75%)	19 (54%)
Pulmonary	10 (36%)	7 (20%)
Renal	9 (32%)	8 (23%)
Sepsis	5 (18%)	6 (17%)
Stroke	4 (14%)	7 (20%)
Total	28 (100%)	35 (100%)

TABLE 8. *Multivariate Analysis of 30-day Mortality*

Variable	Grouping	Adjusted Odds Ratio with 95% CI	p Value
Cardiac arrest	No, Yes	3.64 (0.92, 14.4)	0.069
Year of surgery	58–88, 89–90	0.04 (0.00, 0.44)	0.0003
Cardiac complications	No, Yes	5.53 (1.36, 22.5)	0.014
Dialysis	No, Yes	3.53 (1.08, 11.5)	0.037

CI, confidence interval.

through partial inserted graft. The aneurysm of a 36-year-old woman while being treated for leaking of the upper descending thoracic aortic aneurysm was suddenly entered. The distal aortic arch could not be safely explored for clamping. The bleeding was only partially controlled by pressure until cardiopulmonary bypass was instituted. Perfusion was inadequate to produce hypothermia. The aneurysm was opened, the blood aspirated into heart–lung apparatus. The heart fibrillated, and with circulation arrested, the proximal anastomosis was made between one end of the graft and the distal transverse aortic arch. The arterial perfusion cannula was inserted into the graft, and the air was removed from the proximal aorta and graft. Cardiopulmonary bypass with reinfusion of blood and perfusion of the heart and brachiocephalic vessels was begun. The heart was defibrillated. The distal anastomosis was then completed and circulation was restored to the lower body. The duration of cerebral circulatory arrest in this case was 10 minutes. This patient completely recovered from operation.

Results

Of the 117 patients treated for acute rupture of the descending thoracic and thoracoabdominal aorta, 89 patients (76%) survived 30 days. The causes of early deaths are shown in Table 6. The most common cause of death was cardiac, usually myocardial infarction. All of the 18 patients requiring subtotal replacement of the descending thoracic aorta survived, and 14 (64%) of 22 patients requiring total replacement of the descending thoracic aorta survived operation, as did 57 (74%) of the 77 patients that required thoracoabdominal replacement. Of the seven patients treated by cardiopulmonary bypass, profound hypothermia and circulatory arrest, six (85%) were early (30-day) survivors. All eight patients with aortotracheobronchial and aortoesophageal fistulae were early survivors. Of the 16 patients who had severe hypotension leading to cardiac arrest, nine (56%) were early survivors. Of the seven patients with cardiac arrest who died early, three died before operation was attempted and four died later from cardiac complications, including myocardial infarction and uncontrollable cardiac arrhythmias. Death occurred in only 1 of the 13 patients who had hypotension without cardiac arrest. Morbidity and mortality included pulmonary complications in 55 (51%) associated with death in 36%, stroke complications in 13 (12%) with death in four, reoperation for bleeding in four, wound complications in eight (7%), vocal cord paralysis in nine (8%), renal failure in 21 (19%) and paraplegia or paraparesis in 29 (27%). The results of operation varied during the period of treatment. Ninety-two patients (79%) were treated during the 30-year period from 1958 to 1988. Of these 26 (28%) were early deaths, in contrast to 2 (8%) early deaths in the 25 (21%) treated during the years 1989 to 1990.

TABLE 7. *Univariate Analysis of 30-Day Deaths*

Variable	Odds Ratio	p Value
Cardiac arrest		
No	1	0.0458
Yes	2.96	
Period of operation		
1958–1988	1	0.0353
1989–1990	0.22	
Cardiac complications		
No	1	0.0356
Yes	3.27	
Postoperative hemodialysis		
No	1	0.0060
Yes	4.25	

The significant univariate factors leading to early death in ruptured cases were cardiac arrest, period of operation, postoperative cardiac complications, and postoperative renal failure (Table 7). The significant predictors of early death by multivariate analysis were the same (Table 8). The Kaplan–Meier survival rates at 30 days, 1 year, 2 years, and 5 years in percentages were 76, 58, 48, and 28 respectively (Fig. 4).

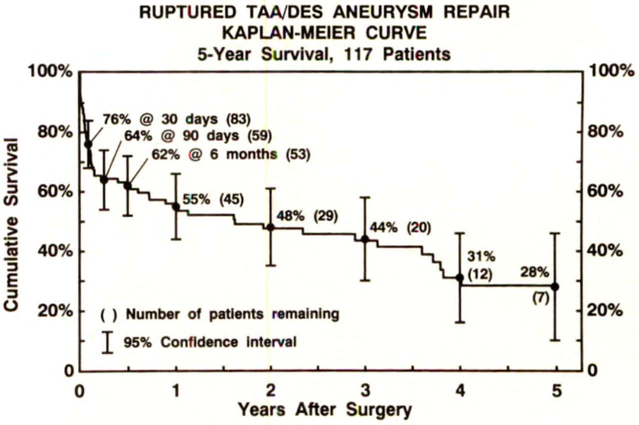


FIG. 4. Five-year Kaplan–Meier survival curve.

TABLE 9. *Ruptured TAA/DES Study*

Outcome Comparison: Ruptured *Versus* Nonruptured

No. of patients	DES	TAA
Ruptured	40	77
Nonruptured	686	1323
30-day mortality rate		
Ruptured	8/40 (20%)	20/77 (26%)
Nonruptured	55/686 (8%)	99/1323 (7%)
Relative risk	2.49	3.47
(95% CI)	(1.28, 4.87)	(2.28, 5.29)
Postoperative paraplegia/paresis*		
Ruptured	8/37 (22%)	21/71 (30%)
Nonruptured	36/677 (5%)	188/1313 (14%)
Relative risk	4.07	2.07
(95% CI)	(2.04, 8.11)	(1.41, 3.03)
Postoperative hemodialysis*		
Ruptured	6/37 (16%)	15/71 (21%)
Nonruptured	18/677 (3%)	95/1313 (7%)
Relative risk	6.10	3.43
(95% CI)	(2.57, 14.5)	(1.87, 6.30)

* In operative survivors.

False aneurysms excluded. Cut-off date was 6/1/90.

CI, confidence interval; DES, descending thoracic aortic aneurysm; TAA, thoracoabdominal aortic aneurysm.

During the period of this study, elective graft replacement was performed in the treatment of 686 patients with aneurysms of the descending thoracic aorta and 1323 patients with thoracoabdominal aortic aneurysms. The differences in 30-day mortality and major complications such as paraplegia or paraparesis and renal failure are shown in Table 9.

Discussion

Rupture of thoracic or thoracoabdominal aortic aneurysms is for the most part a terminal disorder and requires prompt and aggressive treatment. Most of the patients who develop this condition outside the hospital die before appropriate therapy can be instituted. Most of the patients in this study who developed free rupture, hypotension, and cardiac arrest did so in the hospital. Prompt treatment, sometimes innovative, resulted in a highly significant survival rate. The difference in survival rates and rates of morbidity between the large number of patients treated electively and those treated for rupture indicates that the former approach is preferable. This leads to the pertinent question 'When should such aneurysms be treated surgically?' This study of aneurysm size at rupture would suggest that operation should be recommended in patients in whom the aneurysm becomes symptomatic or exceeds 5 cm in diameter as measured by CT scan, and that emergency operation is indicated in patients with signs of blood outside the aortic lumen.

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DISCUSSION

DR. WALTER G. WOLFE (Durham, North Carolina): I hesitate to talk about the last 13 cases of ruptured descending thoracic and thoracoabdominal aneurysms we've had. I will review them briefly because three of the patients died in the operating room and could not be unclamped and died of cardiovascular decompensation.

Of the surviving patients, one had a morbidity-producing stroke, and one had to undergo amputation in the postoperative period. But it is of interest that none of the patients, although they had chemical evidence of renal insufficiency, required dialysis.

Dr. Crawford's paper dots many i's in his outstanding presentation, which will be very interesting reading to all who are interested in this subject, because he goes into great detail management of his case reports, which are instructive as well as overwhelming. I think you will find the manuscript very important to all of you.

If I could see the first slide, please.

Dr. McCann helped me accumulate some data, and this is the second-to-last patient we operated on.

This patient was operated on by Dr. Peter Smith and had the coronary artery bypass grafting 3 years ago and had noted a small aneurysm at that time and presented with pain. And this portable chest x-ray and the next slide shows the CT scan, much like Dr. Crawford's. I included this because it highlights his important point about size. This was clearly not a large aneurysm, and one can see the clot and fluid in both chests in this case.

I show the case because during this operation a transesophageal echo was done. If I could have the next slide.

I'll emphasize, I think, that the transesophageal echo is going to have a more important role in evaluating thoracic aortic disease.

You can see the esophageal probe is here, the aorta here, the flow going away from the probe. This is the aneurysm. And on the dynamic echo we see the blood moving back and forth, blue to orange here, which is very impressive. And this represents a clot.

The next slide, I believe, should have been put in earlier. This is the thoracic aorta up above the point of rupture, and the descending thoracic aorta was ruptured down close to the GE junction.

I wonder if Dr. Crawford might want to comment on transesophageal echo as a mechanism to follow and evaluate descending thoracic and aortic lesions.

I have noticed many of our patients who had previous thoracotomy had obliterated the space, which allowed the patient to survive and get to the operating room.

In these patients, you notice in the atherosclerotic aneurysms, although there is always ulceration and debris within the vessel. These patients have had almost a penetrating ulcer, aside from the other ulcers. A single penetrating ulcer seemed to be the focal point for rupture, which makes me wonder if transesophageal echo might be helpful in detecting small aneurysms in patients with this type of degenerative disease.

The angiographers have described this ulcerative lesion in the aorta, and I wonder if you would comment on that for us.

It appears that once you get these patients to the operating room and get the aorta clamped, that the mortality rate is certainly 25%. This appears to be even less than that in ruptured abdominal aortic aneurysm, which I think is a very interesting and important fact.

DR. BUDDY WILLIAMSON (Tupelo, Mississippi): I thank Dr. Crawford for calling attention to a condition that still remains a stiff challenge for the vascular surgeon, and that is salvaging the patient with a ruptured aortic aneurysm.

Besides being the birthplace of Elvis Presley, Tupelo is the home of the largest rural referral hospital in the country. It is affiliated with the surgical training program in Jackson. We recently examined our 10-year experience with about 52 ruptured abdominal aortic aneurysms that we've done there. We initially had a 38% mortality rate in these patients, but when we further subdivided these patients and looked at our last 5 years, we have been able to reduce this significantly to about 20%.

We've analyzed the factors that we thought were unique to our area and our practice to see if we could come up with what helped us improve in the last 5 years. And some of the important factors that we have been able to highlight include improvement of our rapid transport system and a much more aggressive approach to rapid surgical intervention in the ruptured aneurysm, as well as what we think is maturation and improved experience in our operating teams.

But more importantly, we think now that an aggressive approach to the nonruptured, basically asymptomatic aneurysm can very well be the most significant factor in reducing deaths from ruptured aneurysms.

In view of this, I would like to ask Dr. Crawford his thoughts on a 'find-em-fix-em' approach to the asymptomatic aneurysm. I also would like to know his thoughts on the use of CT scanning in the patient who is highly suspect for the ruptured aneurysm and on any delay that might be taking place in obtaining these scans.

DR. JOSEPH S. COSELLI (Closing discussion): I think there is barely a cardiac surgeon who has done any work at all who has not, on occasion, when operating on a coronary bypass patient, discovered that in the aorta not studied at the time of cardiac catheterization there was a significant dilatation of the ascending aorta. This will then put the surgeon in a position to treat, ignore, or modify his course of therapy, when, in fact, it could have been prevented if the coronary arteriography had been extended into and had fully evaluated the ascending aorta.

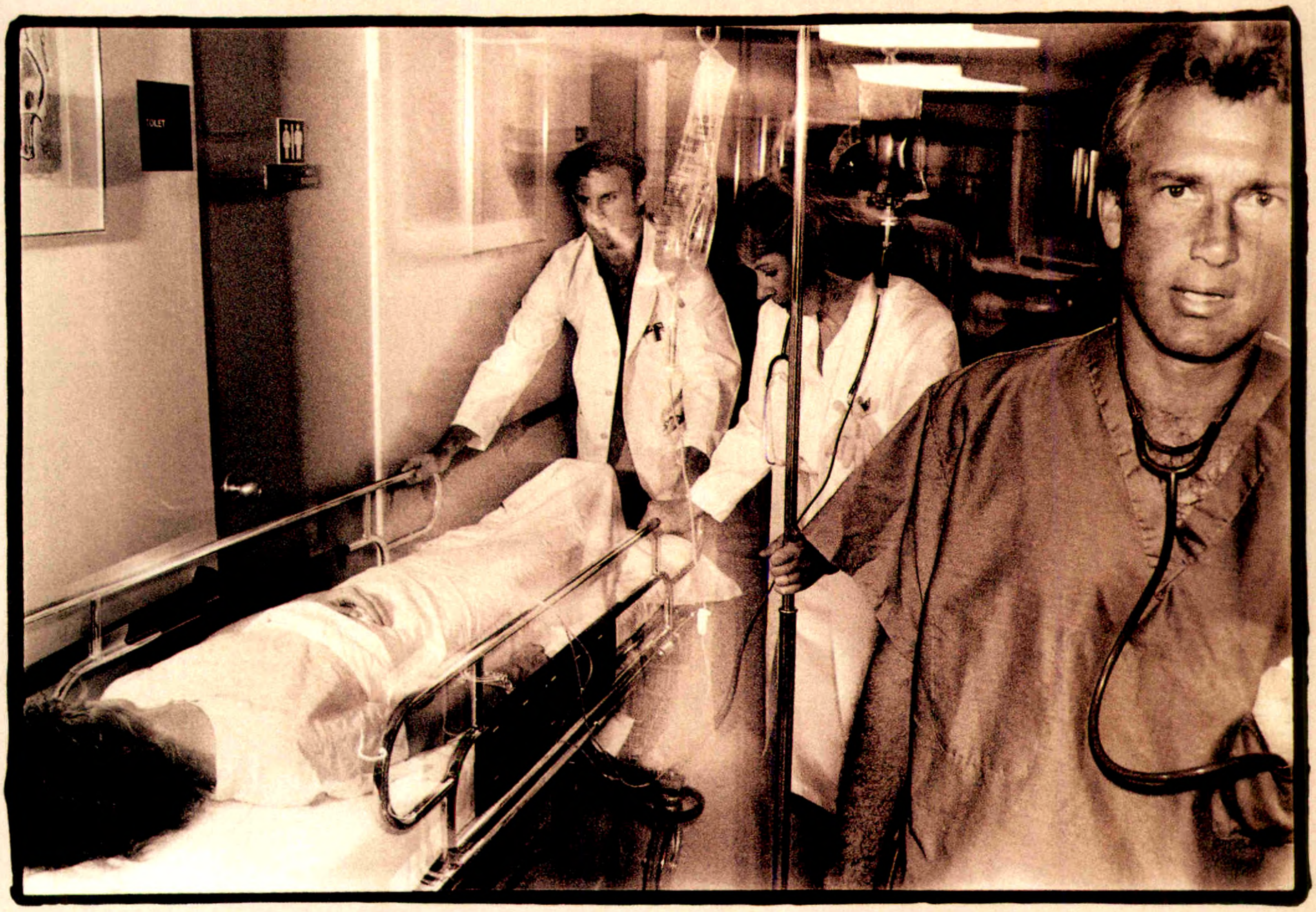
We are using transesophageal echocardiography, both before operation and more and more during operation for evaluation and modification of treatment. Indeed we think that while a patient is undergoing transesophageal echocardiography that particular diagnostic evaluation is not complete until the aorta also has been evaluated using the modality.

In addition two additional points merit further emphasis. In the 114 patients in whom the data were available in this series, the interval between the onset of symptoms suggesting rupture or the change in the nature of the aneurysm varied from less than 1 day to 120 days, with a median of only 3 days.

Second, of the 77 patients with extensive aneurysmal disease involving both the thoracic and abdominal aorta, rupture occurred in the upper abdominal aortic segment in 37 and in the thoracic segment in 40, *i.e.*, about a 50–50 split.

The former reinforces that in patients who cannot be identified and treated on an elective early basis, time is an essential factor and efforts should be expended to bring about expeditiously the initiation of operative intervention.

And the latter validates, I believe, that which Dr. Crawford has championed for years: an aggressive surgical approach that includes a comprehensive replacement of all diseased aortic segments at the initial surgical procedure, *i.e.*, a definitive operation. And this does not, however, necessarily preclude the necessity of course, in selected patients of a planned two-staged treatment.



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INDICATIONS AND USAGE
UNASYN is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below.
Skin and Skin Structure Infections caused by beta-lactamase producing strains of *Staphylococcus aureus*, *Escherichia coli*,* *Klebsiella* spp.* (including *K. pneumoniae**), *Proteus mirabilis*,* *Bacteroides fragilis*,* *Enterobacter* spp.,* and *Acinetobacter calcoaceticus*.*
Intra-Abdominal Infections caused by beta-lactamase producing strains of *Escherichia coli*, *Klebsiella* spp. (including *K. pneumoniae**), *Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.*
Gynecological Infections caused by beta-lactamase producing strains of *Escherichia coli*,* and *Bacteroides* spp.* (including *B. fragilis**).
*Efficacy for this organism in this organ system was studied in fewer than 10 infections.
While UNASYN® (ampicillin sodium/sulbactam sodium) is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with UNASYN due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to UNASYN should not require the addition of another antibiotic.

CONTRAINDICATIONS
The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.

WARNINGS
SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.
SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS
General: A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. In patients treated with UNASYN the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.
Drug Interactions: Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with UNASYN may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with UNASYN and allopurinol administered concurrently. UNASYN and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of UNASYN.
Drug/Laboratory Test Interactions: Administration of UNASYN will result in high urine concentrations of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest™, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Testape™) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriolglucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with UNASYN.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.
Pregnancy
Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See—Drug/Laboratory Test Interactions.)
Labor and Delivery: Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of UNASYN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.
Nursing Mothers: Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman.
Pediatric Use: The efficacy and safety of UNASYN have not been established in infants and children under the age of 12.

ADVERSE REACTIONS
UNASYN is generally well tolerated. The following adverse reactions have been reported.
Local Adverse Reactions
Pain at IM injection site—16% Pain at IV injection site—3%
Thrombophlebitis—3%
Systemic Adverse Reactions
The most frequently reported adverse reactions were diarrhea in 3% of the patients and rash in less than 2% of the patients.
Additional systemic reactions reported in less than 1% of the patients were: itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat, substernal pain, epistaxis and mucosal bleeding.
Adverse Laboratory Changes
Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:
Hepatic: Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH.
Hematologic: Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets.
Blood Chemistry: Decreased serum albumin and total proteins.
Renal: Increased BUN and creatinine.
Urinalysis: Presence of RBC's and hyaline casts in urine.
The following adverse reactions have been reported with ampicillin-class antibiotics and can also occur with UNASYN.
Gastrointestinal: Gastritis, stomatitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.
Hypersensitivity Reactions: Urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with a penicillin (see WARNINGS).
Hematologic: In addition to the adverse laboratory changes listed above for UNASYN, agranulocytosis has been reported during therapy with penicillins. All of these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

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1. Data available on request from Roerig. **2.** Aldridge KE, Sanders CV, Marier RL: Variation in the potentiation of β-lactam antibiotic activity by clavulanic acid and sulbactam against multiply antibiotic-resistant bacteria. *J Antimicrob Chemother* 1986;17:463-469. **3.** Crombleholme WR, Ohm-Smith M, Robbie MO, et al: Ampicillin/sulbactam versus metronidazole-gentamicin in the treatment of soft tissue pelvic infections. *Am J Obstet Gynecol* 1987;156(Feb):507-512. **4.** Cucharal G, Snydman D, Jacobus N, et al: Comparison of new antimicrobial agents against the *Bacteroides fragilis* group. Abstract, presented at the Annual Meeting of the American Society of Microbiology, Miami Beach, Fla; May 1988. **5.** D'Amato RF, Hochstein L, Pavia M: *In vitro* susceptibilities of aerobic and anaerobic clinical isolates to ampicillin/sulbactam. Presented as a Scientific Exhibit at the 87th Annual Meeting of the American Society of Microbiology, Atlanta, March 1987. **6.** Finegold SM: Anaerobic bacteria: Their role in infection and their management. *Postgrad Med* 1987;81(8):141-147. **7.** Jenkins SG: Susceptibility patterns of *Bacteroides fragilis* group isolates to ampicillin/sulbactam and other selected antibiotics. Presented at a symposium entitled *Ampicillin/Sulbactam: New Strategy for the Treatment of Infectious Disease*. Montreux, Switzerland, July 16-17, 1987, pp 19-20. **8.** Tally FP, Jacobus NV: Activity of sulbactam against recent isolates of aerobic and anaerobic bacteria, abstract 36. Presented at the 23rd International Congress of Antimicrobial Agents and Chemotherapy, Las Vegas, Oct 24-26, 1983 (abs). **9.** Wasilauskas B: Susceptibility of anaerobes to ampicillin-sulbactam and 6 other antimicrobial agents, abstract. Presented at the Annual Meeting of the American Society for Microbiology, Miami Beach, Fla, May 8-13, 1988. **10.** Wexler HM, Harris B, Carter WT, et al: In vitro efficacy of sulbactam combined with ampicillin against anaerobic bacteria. *Antimicrob Agents Chemother* 1985;27:876-878. **11.** Ampicillin/sulbactam (Unasyn). *Med Lett Drugs Ther* 1987;29(August 28):79-81. **12.** Hemsell DL, Wendel GD, Hemsell PG: Combating beta-lactamase enzyme—principal defense mechanism of many pelvic infection pathogens. Presented as a scientific exhibit at the Thirty-Sixth Annual Clinical Meeting of the American College of Obstetricians and Gynecologists, Boston, May 2-4, 1988. **13.** Senft H-H, Stiglmayer R, Eibach HW, et al: Sulbactam/ampicillin versus cefoxitin in the treatment of obstetric and gynaecological infections. *Drugs* 1986;31(suppl 2):18-21. **14.** Newton ER, Gibbs RS: Treatment of postpartum endometritis: A comparison of ampicillin/sulbactam vs. gentamicin plus clindamycin. Presented as a scientific exhibit at the Thirty-Sixth Annual Clinical Meeting of the American College of Obstetricians and Gynecologists, Boston, May 2-4, 1988. **15.** Gunning J: A comparison of parenteral sulbactam/ampicillin versus clindamycin/gentamicin in the treatment of pelvic inflammatory disease. *Drugs* 1986;31(suppl 2):14-17. **16.** Stromberg BV, Reines HD, Hunt P: Comparative clinical study of sulbactam and ampicillin and clindamycin and tobramycin in infections of soft tissues. *Surg Gyn Obstet* 1986;162:575-578. **17.** Kager L, Malmborg AS, Nord CE, et al: A randomized controlled trial of ampicillin plus sulbactam vs. gentamicin plus clindamycin in the treatment of intraabdominal infections: A preliminary report. *Rev Infect Dis* 1986;8(suppl 5):S583-S588. **18.** Bruhat MA, Pouly JL, Le Boedec G, et al: Treatment of acute salpingitis with sulbactam/ampicillin: Comparison with cefoxitin. *Drugs* 1986;31(suppl 2):7-10. **19.** Faro S: Experience with ampicillin/sulbactam for OB/GYN infections. Presented at a symposium entitled *β-Lactamase Inhibitors: Progress with Ampicillin/Sulbactam*. Atlanta, December 6, 1987, p 14 (abs).

INDICATIONS AND USAGE
UNASYN is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below.
Skin and Skin Structure Infections caused by beta-lactamase producing strains of *Staphylococcus aureus*, *Escherichia coli*,* *Klebsiella* spp.* (including *K. pneumoniae**), *Proteus mirabilis*,* *Bacteroides fragilis*,* *Enterobacter* spp.,* and *Acinetobacter calcoaceticus*.*
Intra-Abdominal Infections caused by beta-lactamase producing strains of *Escherichia coli*, *Klebsiella* spp. (including *K. pneumoniae**), *Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.*
Gynecological Infections caused by beta-lactamase producing strains of *Escherichia coli*,* and *Bacteroides* spp.* (including *B. fragilis**).
*Efficacy for this organism in this organ system was studied in fewer than 10 infections.
While UNASYN* (ampicillin sodium/sulbactam sodium) is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with UNASYN due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to UNASYN should not require the addition of another antibiotic.

CONTRAINDICATIONS
The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.

WARNINGS
SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.
SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS
General: A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. In patients treated with UNASYN the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.
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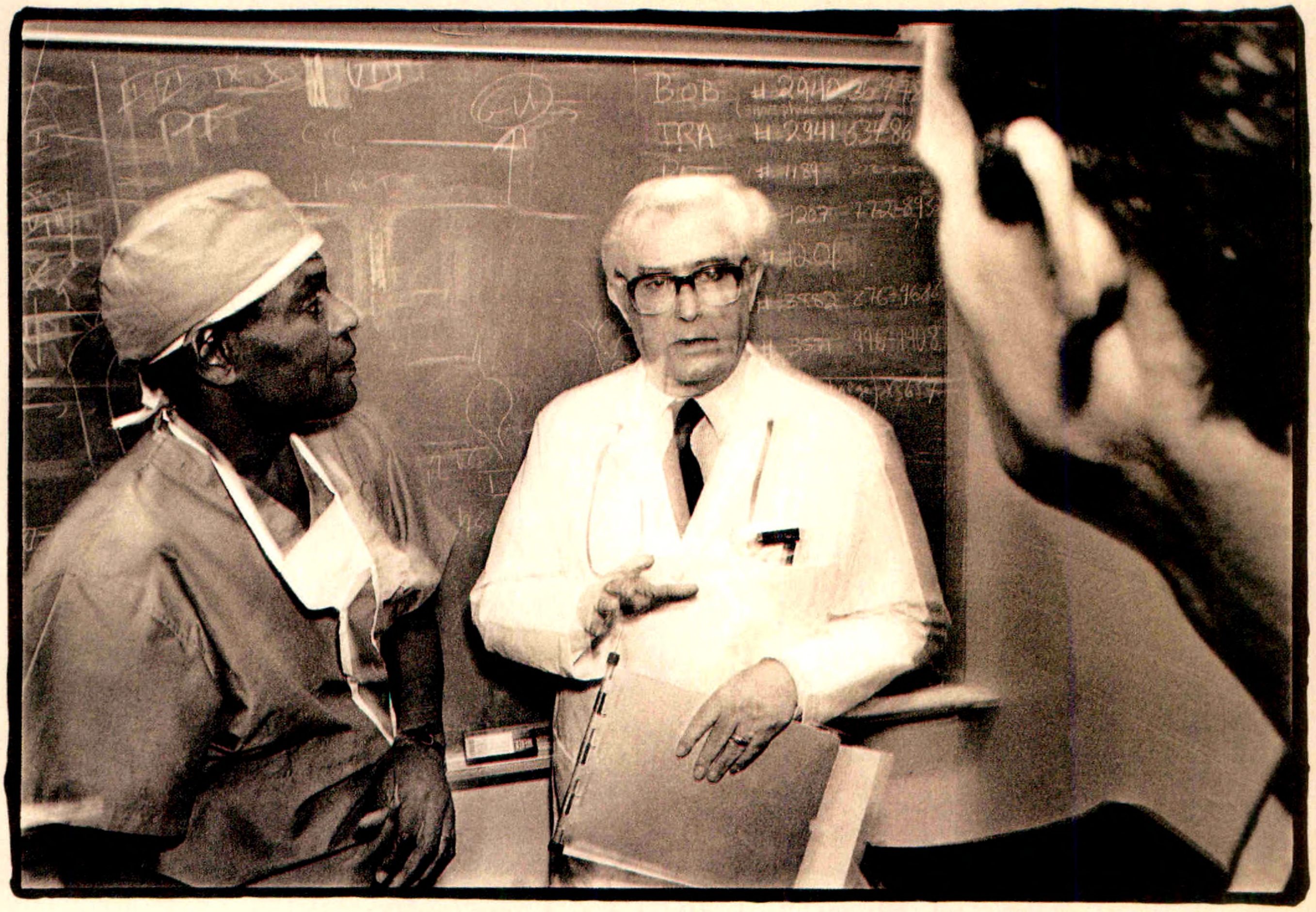

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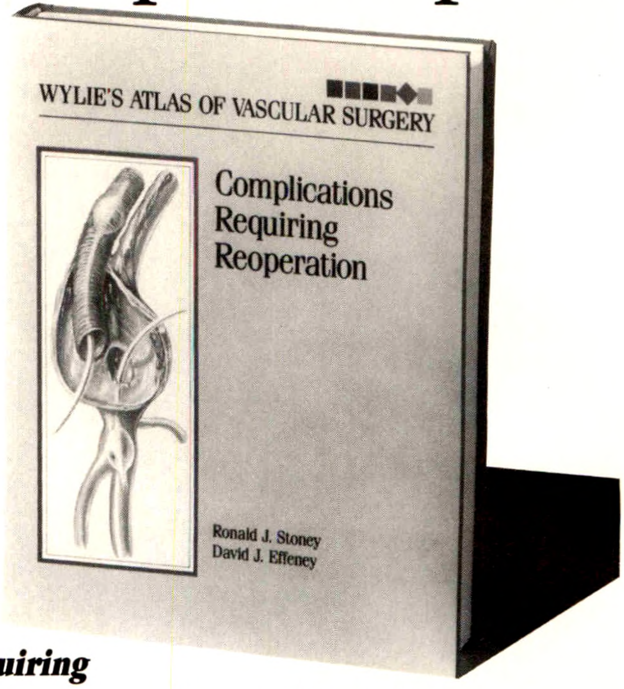

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The Influence of Severity of Spinal Cord Ischemia in the Etiology of Delayed-onset Paraplegia

WILLIAM M. MOORE, JR., M.D., and LARRY H. HOLLIER, M.D., F.A.C.S.

To clarify the cause of delayed-onset paraplegia, the authors evaluated the neurologic outcome after temporary (10 to 30 minutes) spinal cord ischemia in the awake rabbit. Loss of motor function occurred in less than 2 minutes in all animals. Restoration of flow within 16 minutes always resulted in full return of function, whereas with occlusion times of greater than 27 minutes all animals remained paralyzed. After temporary occlusion of 20 to 21 minutes, however, 71% of animals returned to normal neurologic function but developed delayed-onset paraplegia 14 to 48 hours later. This appears to be a reliable method for the creation of a model of delayed-onset paraplegia in the awake animal, and will facilitate more detailed studies of the pathophysiology of ischemia-induced paraplegia.

PARAPLEGIA AFTER REPAIR of extensive thoracoabdominal aortic aneurysms has been reported with a frequency as high as 30% in some series.[1,2] The usual cause of acute spinal cord dysfunction after thoracic aortic occlusion is believed to be spinal cord ischemia from hypoperfusion during cross-clamping. Some patients undergoing thoracoabdominal aneurysm repair, however, awake with no neurologic deficit only to develop delayed-onset paraplegia 1 to 5 days later. The cause of this latter phenomenon is poorly understood, but it has been attributed to postoperative hypotension, embolization to the anterior spinal artery, occlusion of a reimplanted intercostal artery, or anterior spinal artery thrombosis. The precise pathophysiology of this phenomenon, however, has not been identified. The observation of such delayed neurologic deficits suggests the presence of additional mechanisms of spinal cord injury that might include cord edema in a confined space, cytotoxic action from leukocytes or microglia, vasoconstriction from arachidonic acid metabolites, and free-radical injury from metabolic byproducts of ischemia.[3-7]

From the Department of Surgery, Ochsner Clinic and Alton Ochsner Medical Foundation, New Orleans, Louisiana

No reliable animal model of delayed-onset paraplegia has been documented, although previous studies have noted the worsening of neurologic function 24 to 48 hours after spinal cord ischemia in the rabbit model.[8-12] Furthermore because of the anesthetic agents used in the experiments reported, the interrelationships of time of onset and recovery of motor and sensory dysfunction has been inadequately delineated.

We undertook this study to develop a reproducible model for the study of delayed-onset paraplegia in the awake animal and to identify the temporal relationships of motor and sensory changes induced by spinal cord ischemia.

Materials and Methods

Thirty New Zealand white rabbits weighing 4 to 6 kg were premedicated with atropine sulfate (0.005 mg/kg) administered subcutaneously and were anesthetized with intramuscular ketamine hydrochloride (40 mg/kg) and xylazine (3 mg/kg). Intermittent intravenous readministration of one-quarter doses of the anesthetic agents maintained an adequate level of anesthesia and prevented the need for endotracheal intubation and mechanical ventilation. The fur on the chest, abdomen, and back was clipped with electric shears and the skin prepared with Betadine® (Purdue Frederick Co., Norwalk, CT) solution. In the supine position, with the pelvis rotated 45° to the right, an oblique incision was made from the left costal margin directed toward the pubis; this facilitated retroperitoneal dissection and exposure of the infrarenal aorta. The Dunn vascular occlusion device (Solco Basle, Inc., Rockland, MA) was placed around the aorta, immediately inferior to the renal arteries (Fig. 1). The occluder tubing was tunneled, exteriorized, and sutured into a transcu-

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Presented at the 102nd Annual Scientific Session of the Southern Surgical Association, Boca Raton, Florida, December 3-6, 1990.

Address reprint requests to Larry H. Hollier, M.D., Ochsner Clinic, 1514 Jefferson Highway, New Orleans, LA 70121.

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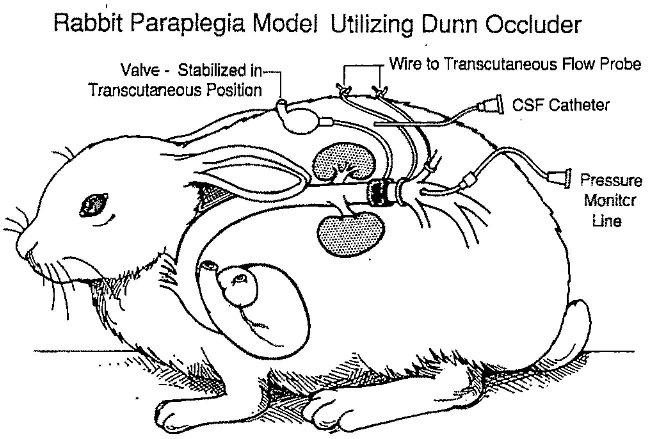
Rabbit Paraplegia Model Utilizing Dunn Occluder
Valve - Stabilized in Transcutaneous Position
Wire to Transcutaneous Flow Probe
CSF Catheter
Pressure Monitor Line

FIG. 1. Schematic diagram of experimental model. The aortic occluder device is positioned around the infrarenal aorta with the inflator valve stabilized in the transcutaneous position.

taneous position just to the left of the paraspinous muscles. The wound was closed in layers with absorbable fascial sutures and nonabsorbable skin sutures. A single dose of buprenorphine hydrochloride (0.1 mg/kg) was administered subcutaneously for postoperative pain control.

Confirmation of aortic occlusion during inflation of the occluder device and of subsequent restitution of distal aortic and lumbar arterial flow was obtained by the placement of electromagnetic and Doppler flow probes in the first five animals. An electromagnetic flow probe of appropriate size (2.5 to 3.5 mm) was secured 1 cm distal to the occluder device. A mini-Doppler flow probe was placed around an infrarenal lumbar artery. The leads from each of these devices were tunneled into a transcutaneous position and coupled to quantitative, directional flow monitors. This method of flow monitoring confirmed cessation of distal aortic and lumbar arterial flow during inflation of the occluder device and restitution of flow after release of the occluder in all five animals tested. Confirmation of return of distal flow after release of the occluder in the remaining animals was obtained by documenting return of femoral pulses.

Forty-eight hours after recovery from anesthesia, two leads of a neurosensory stimulation unit were attached by alligator clips to the skin of the hind limb, and the animal was stimulated every 5 seconds with the lowest voltage required to assess motor and sensory function. Aortic occlusion was then achieved by inflating the circum-aortic occluder with the rabbit in an awake and alert state. The exact times of loss of motor and sensory function after aortic occlusion (*i.e.*, onset of spinal cord ischemia) were recorded.

The aorta was occluded in 30 rabbits (48 trials) for a specified period (10 to 30 minutes), after which restitution of distal flow was permitted (Fig. 2). The neurosensory stimulation was repeated at 15-second intervals and the exact times of motor and sensory function recovery were recorded.

Some of the rabbits that underwent aortic occlusion for brief periods (10 to 16 minutes) experienced quite rapid neurologic recovery and were therefore selected for reocclusion after a period of rest of at least 7 days, resulting in a total of 48 trials in 30 rabbits.

The animals were killed after documentation of irreversible paraplegia or at the completion of the project. Killing was performed with a lethal intravenous dose of phenobarbital and potassium chloride. After death, representative animals from each group of clinical outcomes underwent detailed pathologic examination of the aorta, lumbar arteries, and spinal cord, the latter of which were fixed in formalin and examined microscopically after hematoxylin and eosin staining.

Animal handling, care, and disposal conformed to the guidelines set forth in the "Principles of Laboratory Animal Care" and the "Guide for the Care and Use of Laboratory Animals" (National Institutes of Health publication no. 86-23, revised 1985).

The data were subjected to standard statistical analyses using the nonpaired Student's t test, chi square, one-sided Fisher's exact test, and linear regression analysis.

Results

Level of Ultimate Neurologic Function

All trials of aortic occlusion resulted in spinal cord ischemia that led to total loss of motor and sensory function that persisted throughout the period of aortic occlusion (10 to 30 minutes). After restoration of blood flow, the clinical course of each animal was observed and could be categorized retrospectively into three groups. After brief periods of spinal cord ischemia (less than 17 minutes, group I, n = 11) the loss of hind limb neurologic function was reversible and resulted in permanent return of normal

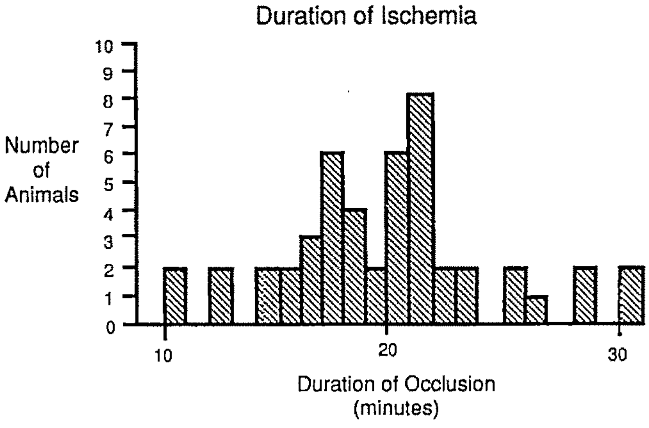

FIG. 2. Graph showing the number of trials for each specific time period of aortic occlusion.

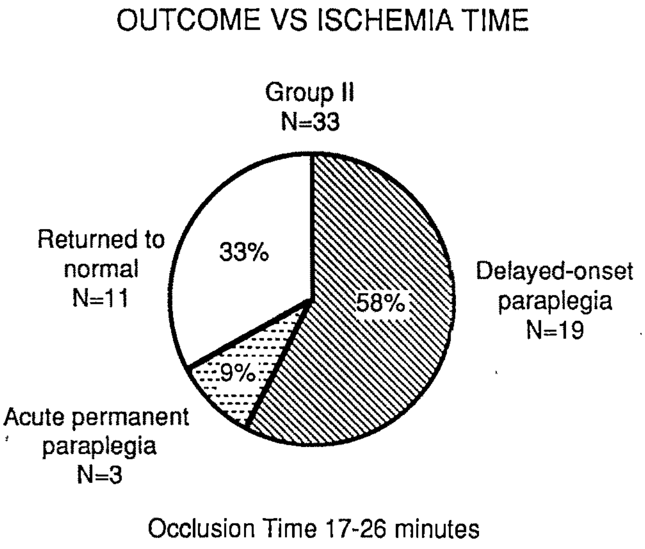

FIG. 3. Graph illustrating the neurologic outcome of the 33 animals that underwent occlusion times from 17 to 26 minutes. Fifty-eight per cent of these animals had return of normal neurologic function after occlusion but subsequently developed delayed-onset paraplegia.

neurologic function after reperfusion ($p < 0.001$). Loss of bladder and anal sphincter control was also noted, but likewise was reversible after brief periods of ischemia, corresponding to the recovery period of hind limb function.

After prolonged periods of spinal cord ischemia (more than 27 minutes, group III, $n = 4$) irreversible paraplegia was observed in all trials ($p < 0.05$).

Intermediate periods of spinal cord ischemia (17 to 26 minutes, group II, $n = 33$) resulted in three ultimate neurologic outcomes (Fig. 3). The first outcome was full return of neurologic function, as had been observed in all trials in group I. There were 11 of 33 trials (33.3%) that resulted in persistent, normal neurologic function after reperfusion. The second outcome was permanent, irreversible paraplegia noted in 3 of 33 trials (9%), as observed in all trials in group III. The third neurologic outcome observed in group II was delayed-onset paraplegia in 19 of 33 trials (57.6%). This subgroup of rabbits regained normal hind limb motor and sensory function, as well as normal bowel and bladder sphincter function after spinal cord reperfusion; however 14 to 48 hours (mean, 27 hours) after reperfusion, these rabbits developed delayed-onset, permanent paraplegia with loss of bowel and bladder sphincter control. Sensation of pain and coarse touch were retained in all animals experiencing delayed-onset paraplegia.

Linear regression analysis of these data confirm a direct relationship between the duration of spinal cord ischemia and ultimate neurologic outcome, correlation coefficient $r = 0.65$ ($p < 0.0001$). The incidence of delayed-onset paraplegia was highest after aortic occlusion periods of 20 and 21 minutes; therefore, this subgroup was subjected to independent analysis. After 20 to 21 minutes of ischemia, delayed-onset paraplegia occurred in 10 of 14 trials (71.4%), acute/permanent paraplegia in 2 of 14 trials (14.3%), and reversed/normal in 2 of 14 trials (14.3%) (Fig. 4). Linear regression analysis predicts an outcome of delayed-onset paraplegia after 20 to 21 minutes of spinal cord ischemia in over 70% of trials, with 95% confidence.

Onset and Recovery of Neurologic Dysfunction

The period between initiation of spinal cord ischemia and onset of motor and sensory dysfunction was analyzed. Because all 48 trials were identical with regard to this feature, pooled results from all three groups were analyzed. Loss of motor function occurred 10 to 120 seconds after aortic occlusion (mean, 55 seconds; $n = 48$). Loss of sensory function occurred 40 to 270 seconds after aortic occlusion (mean, 114 seconds; $n = 32$). Although there was variation in time until onset of deficits between the trials, motor loss preceded sensory loss in 100% of the trials. In an analysis of the means using an unpaired Student's t test, the time difference between onset of motor *versus* sensory loss is statistically significant ($p < 0.001$).

The time required for motor and sensory recovery in group II trials was analyzed in a similar fashion. The time required for full recovery of motor function ranged from 5 to 210 minutes (mean, 53 minutes; standard error, 11.4 minutes). The time required for recovery of sensory function ranged from 2 to 20 minutes (mean, 9 minutes; standard error, 1.7 minutes). Recovery of sensory function occurred before recovery of motor function in 100% of the trials, and the difference in the time interval required for recovery of sensory *versus* motor function is significantly different ($p < 0.001$) (Fig. 5).

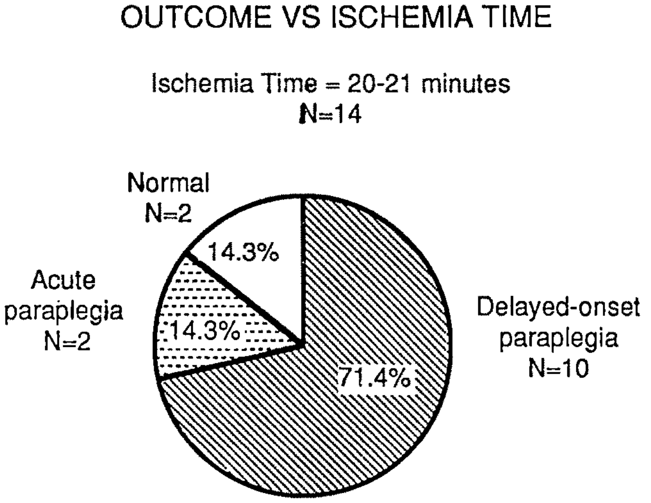

FIG. 4. Graph showing the incidence of delayed-onset paraplegia associated with a spinal cord ischemia time of 20 to 21 minutes.

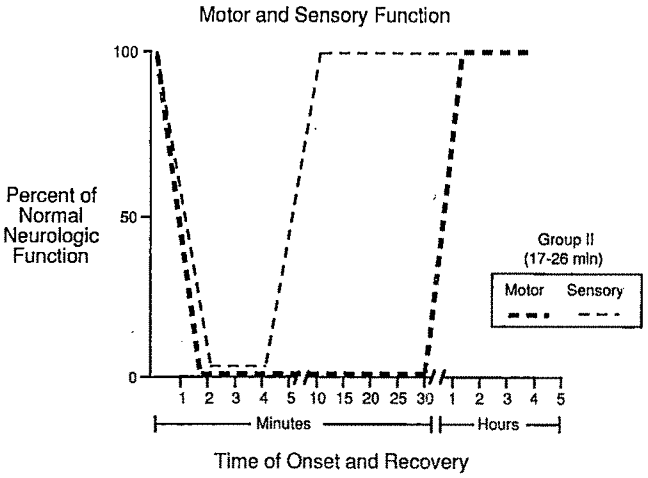

FIG. 5. Graph showing the relative time of onset and recovery of motor *versus* sensory function associated with spinal cord ischemia in the Group II animals.

An analysis of means was conducted between groups I and II with regard to recovery of motor function. The mean time required for full recovery of motor function in group I was 27 minutes (all animals reversed to normal), and in group II was 53 minutes (33% reversed to normal; 58% reversed to normal, then subsequently experienced delayed-onset paraplegia; and 9% experienced acute, permanent paraplegia.) (Fig. 3). The difference between 27 and 53 minutes is significant ($p < 0.01$). Therefore the time required for return of full motor function after temporary spinal cord ischemia is predictive of resultant neurologic outcome.

Pathologic Findings

Pathologic examination of the animals after death was undertaken specifically to determine if paraplegia or delayed-onset paraplegia was related to thrombosis (acute or late) of the aorta or the lumbar arteries. In no animal was there any evidence of thrombosis of these vessels nor was there any evidence of embolization.

Histologic examination of the spinal cord permitted comparison of normal cord with the spinal cord of rabbits experiencing each of the three potential neurologic outcomes. Specimens of rabbits experiencing sustained recovery of neurologic function showed normal numbers of ganglion cells with normal nuclei and cytoplasm. Evaluation of spinal cord specimens from rabbits experiencing delayed-onset paraplegia showed decreased staining of ganglion cells. Many of the ganglion cells identified had hyperchromatic nuclei and mild to moderate vacuolization of cytoplasm. Diffuse destruction of gray matter with moderate to severe vacuolization and essentially no normal ganglion cells was observed in the spinal cord of rabbits experiencing acute, permanent paraplegia.

Discussion

In the human, as well as in most animal models, prolonged clamping of the thoracic aorta can result in paraplegia. Because of the tremendous variability in the adequacy of collaterals to the spinal cord, however, the predictability of neurologic outcome after aortic cross-clamping is poor; this also makes prediction of the severity of neurologic injury difficult. Therefore a reliable model of defined ischemic spinal cord injury would be very helpful in studying the pathophysiology of both acute and delayed-onset paraplegia.

Other problems complicating attempts to study the variables associated with paraplegia are the marked hemodynamic and other physiologic changes associated with thoracic aortic cross-clamping. Because the rabbit has a segmented arterial supply to the spinal cord, occlusion of the infrarenal aorta will result in spinal cord ischemia, but is associated with minimal hemodynamic variation. Furthermore allowing the rabbit to recover after implantation of the occluder device permits evaluation of the responses to spinal cord ischemia in the awake model so that both sensory and motor neurologic changes can be assessed.

It is interesting to note that in these experiments, motor function was always lost before sensory loss, and sensory return always occurred before return of motor function. This may reflect an increased sensitivity to ischemia of anterior horn cells and motor tracts when compared with dorsal columns. We made no attempt to determine if blood flow during the time of ischemia differed from one area to another within a given segment of ischemic cord, although we did document such differential blood flows in the dog model.[13]

When one compares the time required for return of motor function after unclamping between those animals that developed delayed-onset paraplegia and those that recovered and maintained normal neurologic function, the difference is significant ($p < 0.01$). The mean time until motor recovery in those animals that developed delayed-onset paraplegia (59 minutes) was two times greater than the motor recovery time of those that had permanent recovery (25 minutes).

Sensory recovery did occur in all animals, even in those that sustained acute permanent paraplegia, but return of sensory function occurred later in those that developed acute paraplegia (20 minutes) than in those that experienced permanent recovery (8.5 minutes). This observation did not reach statistical significance because of the small sample size. It would appear, however, that the clinical usefulness of these findings is negligible.

This study clearly documented that paraplegia in the rabbit could be caused by spinal cord ischemia after as little as 10 seconds, but was reliably reversible after as

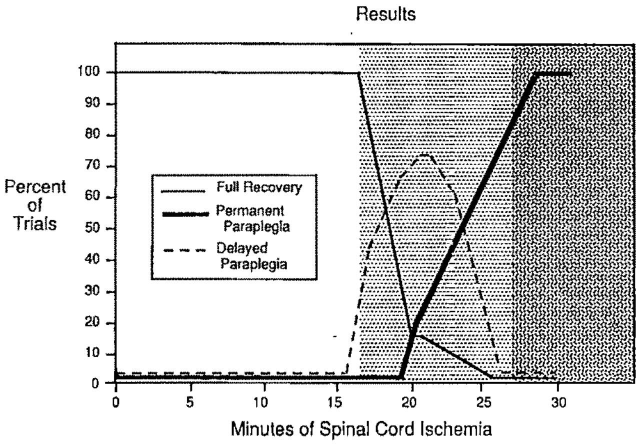

FIG. 6. Schematic graph illustrating the relationship of ultimate neurologic outcome in relation to duration of spinal cord ischemia.

much as 16 minutes of ischemia. It also showed that prolonged spinal cord ischemia in the rabbit, in other words, more than 27 minutes, will reliably produce acute, permanent paraplegia.

An intermediate level of spinal cord ischemia in the rabbit, in other words, 20 to 21 minutes, will usually result in full return of neurologic function after restoration of blood flow to the spinal cord, and the rabbit will be able to hop normally and will show no functional change; however, this is often (71%) followed by the onset of recurrent and progressive paraplegia within 14 to 48 hours (Fig. 6). The observation of delayed-onset paraplegia in this model is important because it documents that this phenomenon is primarily related to the duration or severity of the initial ischemic event and is not likely due to thrombosis or embolization of spinal arteries, nor to postoperative hypotension, as has been occasionally suggested in cases of delayed-onset paraplegia in humans. It is clear that, at least in the rabbit model, delayed-onset paraplegia can occur without antecedent thrombosis or hemodynamic dysfunction.

The precise cause of delayed-onset paraplegia remains unresolved. One must postulate, however, that cellular and metabolic dysfunction initiated by ischemia, as well as delayed hyperperfusion with resultant cord edema in a closed space, may all have a role in causing delayed-onset paraplegia.[14]

This paper documents a reliable method for the creation of delayed-onset paraplegia in the awake animal. This model will facilitate more detailed studies of the pathophysiology of ischemia-induced paraplegia and will allow the evaluation of those therapeutic modalities that may be beneficial in reducing the incidence of this dreaded surgical complication.

Acknowledgments

The authors thank Barbara Siede for assistance in the preparation of the illustrations and Gail Guidry for assistance in the preparation of the manuscript.

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DISCUSSION

DR. H. EDWARD GARRETT (Memphis, Tennessee): Dr. Crawford has led the way in the management of this devastating lesion and Dr. Hollier has continued to seek explanations for the dreaded complication of paraplegia.

Dr. Hollier now presents an experimental model to study further ischemia of the spinal cord and perhaps lead to preventive therapy.

We are all greatly indebted to these members of the Southern Surgical Association for their efforts and their contribution.

DR. E. STANLEY CRAWFORD (Houston, Texas): This model that Dr. Hollier and his group have developed provides an excellent opportunity to try many of the options available to determine if the incidence of paraplegia can be reduced. One of the most truly disappointing characteristics of this disorder is its appearance after a patient has done very well for several days—and in our experience, up to 3 weeks after operation.

There is no question that cardiac hemodynamic changes produce the disturbance in some patients. For example, a patient can suffer a bleed from the gastrointestinal tract, go into shock, and become paraplegic. When his or her blood volume is restored, the paraplegia will disappear, returning when bleeding begins again and then relieved with transfusion. This presents pretty clear evidence to me that, in this particular case, paraplegia was due to hemodynamic changes.

Another case is of a patient doing well who develops a cardiac rhythm problem, a very fast rate, poor cardiac output, and then develops paraplegia. When the rhythm problem is resolved with the return of good cardiac output, paraplegia disappears; this indicates to me that there was a pump problem.

In the patient whose endotracheal tube is removed and who develops anoxia from poor respiration followed by the development of paraplegia, the paraplegia resolves with reintubation and restoration of respiratory mechanics—evidence that there was an anoxic reason.

However there are some patients who develop this problem for which there are absolutely no explanations, which brings up the possibility of reperfusion injury. Therefore I think this would be an excellent model with which to test these agents.

The final significance, at least in our experience, is the fact that these delayed occurrences account for one third to one half of the incidence of paraplegia, depending on the period in the series within which it occurs. If we can determine how to prevent even the delayed cases, we would decrease the incidence of neurologic deficits significantly.

DR. LARRY HOLLIER (Closing discussion): I agree with Dr. Crawford that the occurrence of this phenomenon does comprise a significant number of the postoperative neurologic deficits that occur in relation to the spinal cord.

Clearly some of those patients develop this because of hemodynamic factors that occur after operation. As he stated, there are some patients, however, who develop this with no other reasonable explanation other than some type of a reperfusion injury.

We hope that by use of a reliable reproduceable model, we can extend the study to look at multiple factors, which, as isolated therapeutic modalities, have had very little benefit in preventing paraplegia. But perhaps if we use all possible adjunctive therapies together, we can help reduce this in these difficult cases.

Evaluating Quality, Cost-effective Health Care

Vascular Database Predicated on Hospital Discharge Abstracts

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This population-based study examines all carotid endarterectomies (CE) performed by all surgeons in a single state over a 10-year period. The methodology is designed to determine morbidity rate, mortality rate, cost, and length of stay, as well as to understand the effect of pre-existing chronic disease, physician, and hospital volume on these outcome variables. The data source consisted of hospital discharge abstract data uniformly collected on all admissions (N = 5.9 million) to acute care hospitals in the state. In the decade 1979 to 1988, 11,199 patients underwent CE. Mortality rate from CE was 2.1%, and the postoperative stroke rate was 3.7% over this period. High physician volume decreased the mortality rate ($p < 0.05$) and stroke rate ($p < 0.01$) by 50% and significantly ($p < 0.001$) reduced hospital cost and length of stay independent of patient complexity. Examination of cost data, adjusted for inflation, showed a decrease in mean cost for CE over the decade. Thus physicians are providing better care for less hospital dollars. Both patient and payor outcome is improved by concentrating CE patients in the hands of high-volume surgeons. Although the data suggests this trend is already evolving, the pace of this evolution can be expected to increase as payors recognize that regionalization of this procedure lowers costs.

ATHEROSCLEROSIS IS A chronic homogeneous disease variable only by severity and socioeconomic impact. Historically older adults with positive cardiovascular risk factors have suffered the consequences of this devastating process. Through the years both surgical and medical advances have improved patient survival and quality of life.

Extracranial carotid atherosclerosis (CA) with resulting cerebral ischemia or infarction is the third leading cause of death in North America.[1,2] If not initially fatal, stroke may cause permanent functional impairment. Carotid endarterectomy (CE) was introduced four decades ago for relief of extracranial CA.[3] It is now the most frequently performed peripheral vascular operation, despite its controversial value in stroke prevention.[4]

Current reports on outcome of CE contain disparities in morbidity and mortality rates dependent on operative indication, surgeon experience, and geography of service.[5–8] No population-based study defines patient outcome and addresses cost issues for CE. The health care delivery system in the United States must contain rising expenditures; therefore the indications for all surgical procedures are being examined to identify cost efficiencies. All parties, patient, provider, and payor are clamoring for the delivery of quality, effective care for the fewest dollars.[9] Physicians must address these issues or risk restrictions on their ability to practice.

Methods

Data Source

The study data source consisted of computerized hospital discharge abstract data uniformly collected on all discharges from acute care hospitals in a single state between January 1, 1979 and December 31, 1988. This database includes the following: patient demographics, type of admission, length of stay, discharge status, and five diagnoses and three procedures codes using the International Classification of Disease, 9th Revision, Clinical Modification ICD-9-CM.[10] In addition, each hospital and physician was represented by a coded value. Changes in physician identification codes were made in mid-1985, which permitted double counting of physician operations. This structural variation in the database disqualifies 1985 data for physician volume analysis.

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The Study Population

Patients undergoing carotid endarterectomy were defined as having a procedure code ICD-9-CM, 38.12, (endarterectomy with embolectomy, patch graft, temporary bypass, or thrombectomy of intracranial vessels). Thirty-two patients (0.3%) less than 30 years old, or who had bed service listed as obstetrics, newborn, pediatric, psychiatry, or rehabilitation clearly represented coding errors and were excluded. Over the 10-year period there were 5,981,941 hospital admissions. Of these 11,199 patients underwent carotid endarterectomy and form the basis of this study.

Definition of Terms

Mortality: Defined as in-hospital death. No information is available from the database about long-term follow-up.

Stroke: Patients with ICD-9-CM codes 434.0, 434.1, and 431.9 (occlusion of cerebral arteries) and 997.0 (central nervous system complications resulting from procedure) were defined as in-hospital stroke.

Costs: Total hospital charges by cost centers were provided in the abstracted data. Because of the unique and stndardized system of costs-to-charge ratios used throughout the state, hospital charges can be taken for a proxy for costs to the hospital. This figure does not, however, include physician charges or postoperative follow-up.

Length of Stay (LOS): defined as the number of days in the hospital during which the carotid endarerectomy was performed.

Pre-existing Conditions (PEC): Chronic medical conditions that were coded as secondary diagnoses on the hospital discharge abstract. Four pre-existing medical conditions were considered to potentially complicate a patient's hospital course: ischemic heart disease, chronic obstructive pulmonary disease, diabetes mellitus, and hypertension (Table 1).

Physician Volume: Each physician in the state was assigned a numerical identification code associated with each operative procedure. All physicians performing endarterectomies in the state were then grouped according to the volume of CEs performed in a given year. Each year a physician was assigned to either low-, medium-, or high-volume groups based on the number of CEs in that year. Low-volume physicians were defined as performing between 1 and 12 CEs. Medium-volume physicians performed 13 to 49 procedures, and high-volume physicians (HVP) performed 50 or more procedures in a given year.

TABLE 1. *Pre-existing Conditions (PEC)*

PEC	N (%)	ICD-9CM Code
Hypertension	3,241 (28.9)	401–405
Ischemic heart disease	1,736 (15.5)	411–414
Diabetes	1,473 (13.2)	250
COPD	707 (6.3)	490–496

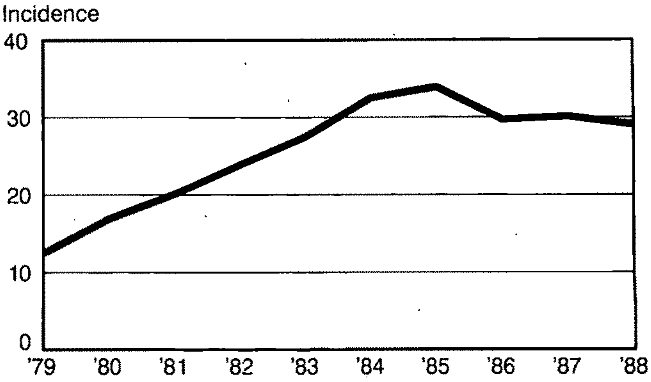

FIG. 1. Incidence of carotid endarterectomies/100,000 population.

Hospital Volume: Each hospital within the state was assigned a unique identifier code. To determine the system effect distinct from physician technique, patient outcome was examined as a function of hospital volume. Hospitals were assigned to high, medium, or low volume based on the number of CEs performed in a given year. High volume was defined as over 50 procedures a year (mid-volume, 13 to 49; and low volume, 1 to 12 CEs). It is possible for an individual hospital, or physician to change volume groups from 1 year to the next.

Statistical Analysis

The yearly incidence of CE was calculated by dividing the number of persons undergoing the procedure by the state population as reported by the state's department of planning. Dichotomous outcome indicators for patients undergoing CE by low-, middle-, or high-volume institutions for physicians were compared using 2 × 3 chi square tests. In addition, low- and high-volume hospital procedures were compared using 2 × 2 chi square tests. Differences in continuous outcome variables (length of stay and cost) were tested using analysis of variance, and a linear contrast was performed to test the low *versus* high hospital and physician volume procedures. For outcome by volume and PEC analysis, separate chi square tests were performed for patients with a PEC and for the overall study population.[11]

Results

Over a 10-year period, 11,199 patients underwent CE in a single state. Two hundred thirty-one patients died (2.1%) and 415 patients (3.7%) suffered a stroke before discharge. The mean length of stay for the entire population was 11.2 days. The mean cost per patient over the

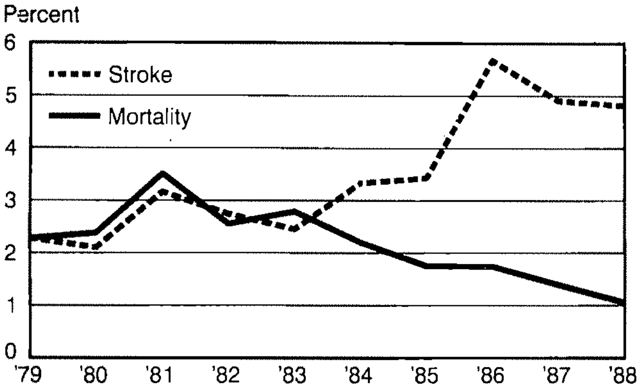

FIG. 2. Peak in stroke rate occurred in 1986.

10-year period was $6150.00, and the total cost for CE during the 10-year period was $68.8 million.

Figure 1 demonstrates the incidence of CE per 100,000 population. The incidence increases through the year 1985, and then remains stable for the last 4 years of the study. Figure 2 contrasts the declining mortality rate with the increasing rate of postoperative stroke. The stroke rate in the last year of the study was 4.8%, whereas the mortality rate in the final year of the study was 1.05%.

The mean LOS for CE over the 10-year period steadily decreases, from a peak of 15.5 days in 1979 to a nadir of 7.7 days in 1988 ($p < 0.001$). The majority of this improvement in mean hospital stay is attributable to the decrease in the number of patients who had an extended hospital stay of over 21 days. In 1979, 20% of patients were in the hospital for 21 days or more. In 1988, that number had decreased to 5.3%. Although costs increase from 1979 to 1983, they have remained relatively stable since 1983. When this increase in costs is plotted as a function of the consumer price index[12] (Fig. 3), a measurement of inflation, we see that despite the rising incidence of CE, the mean patient cost to society in 1979 dollars is less in 1988 than it was in 1979.

Complex Patients

We defined patients with one or more PECs as complex patients. Forty-eight per cent of the patients (5379) patients were defined as complex (48%). Table 1 demonstrates the relative incidence of the various PECs. Figure 4 demonstrates that age and the incidence of complex patients increases over time.

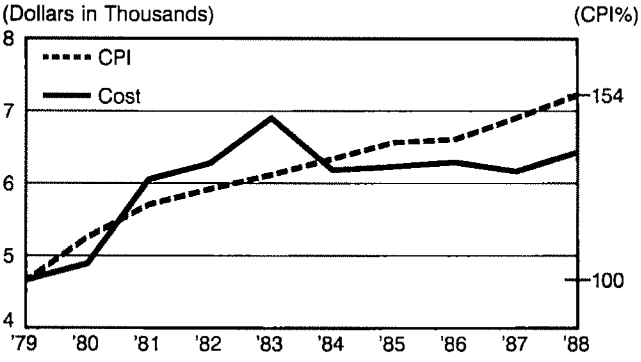

FIG. 3. Level cost curve for carotid endarterectomies for four years.

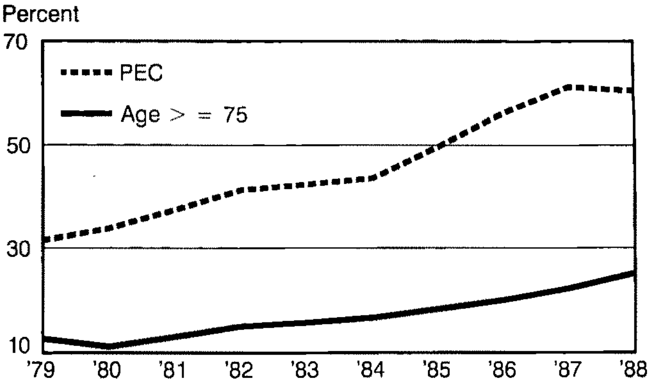

FIG. 4. Increasing age and number of complex patients. PEC, pre-existing condition.

Table 2 demonstrates the effect of PECs on mortality rate, stroke rate, length of stay, and cost. There were no significant differences in mortality rate, stroke, or length of stay as a function of PEC. The intensity of services rendered in PEC-positive patients during their hospital stay, however, accounts for approximately $700 increased cost for PEC-positive patients ($p = 0.0001$).

The distribution of patients with PECs by physician volume suggests that over time complex patients are increasingly referred to HVPs. This suggests an effective triage mechanism is developing, initiated either by the referring physician or the patient. During this period, however, there were still over 2700 (51.2%) complex patients who had their CE performed by a low-volume physician.

Volume/Quality

The 190 physicians annually performing CE over this 10-year period were stratified by volume. Figure 5 is a stacked histogram showing the distribution of patients to low-volume physicians (LVPs) over time, suggesting that LVPs are losing market share.

Table 3 demonstrates that mortality ($p < 0.05$) and

TABLE 2. *Outcome Indicators by the Presence of Pre-existing Conditions*

	Pre-existing Conditions		
	No	Yes	p value
N	5820	5379	
Mortality	132	99	0.11
(Column %)	(2.27)	(1.84)	
Stroke	216	199	NS
(Column %)	(3.71)	(3.70)	
Mean length of stay	11.4	11.07	0.105
Mean cost	$5,802	$6,526	0.0001

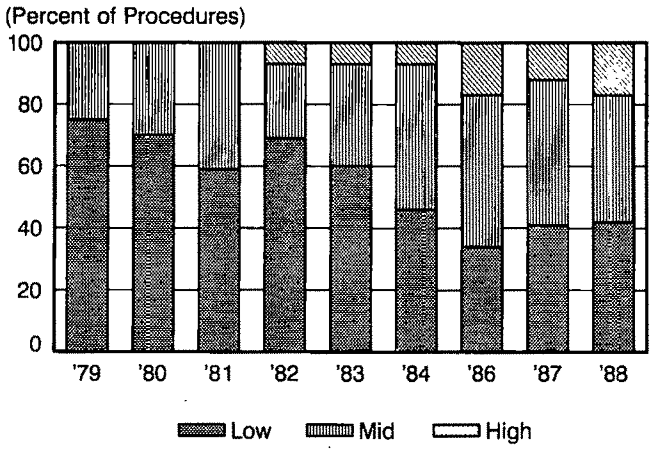

FIG. 5. Distribution of patients showing HVPs assuming a larger market share. The year 1985 is omitted because of double counting.

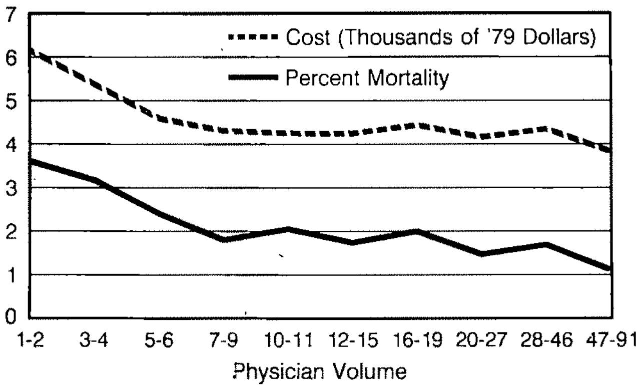

FIG. 6. Mortality rate and cost by decile of physician volume.

stroke rates ($p < 0.01$) decrease by 50% as a function of physician volume. In addition physician volume significantly ($p < 0.001$) lowers LOS and cost. Low-volume physicians increase the mean cost of operation by more than $1000.00.

Figure 6 presents outcome data on mortality rate and cost by decile of physician volume, excluding 1985 (n = 9715). Forty per cent of CEs were performed by physicians whose volume was less than 10 procedures a year. Mortality rate decreases precipitously until physician volume reaches nine CEs per year, and then mortality rate decreases more slowly. Hospital cost as a function of physician volume by decile suggests a minimum yearly volume of nine is required to be cost efficient.

To judge the relative influence of physician technique *versus* system efficiency on outcome, a similar analysis was performed using hospital volume. All hospitals performing carotid endarterectomy were analyzed by CE volume. Figure 7 is a stacked histogram depicting grouped hospital volume over time. There is an increasing trend for CE to be performed in higher-volume hospitals.

Table 4 presents outcome criteria by hospital volume for all patients and complex patients. There are no statistically significant differences between mortality rate and postoperative stroke rate on the basis of hospital volume. Increased hospital volume is associated with decreased length of stay ($p < 0.001$) and cost ($p = 0.05$).

TABLE 3. *Outcome by Physician Volume*

	Low	Mid	High	p-value L *vs* H
N				
Overall	5067	3876	772	
Complex	2289 (45.2)	1887 (48.7)	466 (60.4)	<0.001
Mortality (%)				
Overall	130 (2.6)	66 (1.7)	9 (1.2)	0.02
Complex	60 (2.6)	27 (1.4)	4 (0.9)	0.02
Stroke (%)				
Overall	203 (4.0)	145 (3.7)	16 (2.1)	0.008
Complex	100 (4.4)	68 (3.6)	8 (1.7)	0.007
Length of stay				
Overall	12.7	10.5	8.1	<0.001
Complex	13.1	9.9	7.9	<0.001
Cost				
Overall	$6531	$5746	$5520	<0.001
Complex	$7355	$5824	$5798	<0.001

Discussion

Historically outcome data for CE has emanated from a small group of surgeons interested in the procedure. This study examines CE performed by a large number of unselected surgeons over a 10-year period. This population-based approach is designed to define morbidity rate, mortality rate, LOS, and cost. It is only in using this methodology that policy decisions can be made regarding the efficacy of CE.

The data demonstrates that the incidence of CE increases steadily during a decade as operative indications expand to include older and more complex patients. Despite this increase in complexity, operative mortality decreases but postoperative stroke rate increases. It is spec-

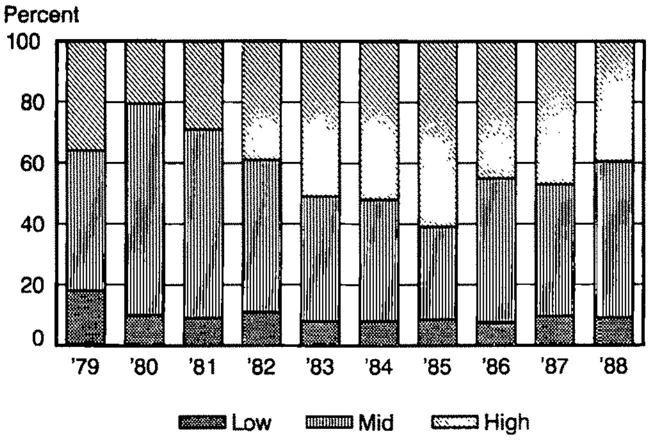

FIG. 7. Stacked histogram of hospital volume.

TABLE 4. *Outcome by Hospital Volume*

	Low	Mid	High	p-value L *vs* H
N				
	922	5,258	5,019	
Overall	420	2,372	2,587	
Complex	(45.6)	(45.1)	(51.5)	0.001
Mortality				
Overall	22 (2.4)	117 (2.2)	92 (1.8)	NS
Complex	5 (1.2)	50 (2.1)	44 (1.7)	NS
Stroke				
Overall	33 (3.6)	205 (3.9)	177 (3.5)	NS
Complex	19 (4.5)	98 (4.1)	82 (3.2)	NS
Length of stay				
Overall	12.9	12.2	10.0	<0.001
Complex	13.1	12.2	9.7	<0.001
Cost				
Overall	$6504	$6353	$5872	0.004
Complex	$6774	$6913	$6131	0.053

ulated that there is a correlation between the increase in stroke rate and the complexity of the patient population; however the data neither confirms or denies our speculation.

Traditionally, physicians have evaluated surgical procedures by clinical outcome. With increasing attention on resource allocation, CE also was analyzed by cost during the decade. Although both mean cost and the total cost increase, the increased total cost results from a growing number of patients undergoing CE. When adjusted for inflation, the mean cost per year for CE decreases during the decade. Increased operative incidence for less cost indicates increased provider productivity. Thus, despite increasing numbers of CEs performed and improved quality, as reflected by decreasing mortality, the cost per operation decreases. This demonstrates that physicians are providing better care for less hospital dollars, in other words, increased productivity. Contrary to political rhetoric, the medical community has improved both the productivity and efficiency of CE. This increased productivity occurred in a decade when total medical costs have continuously increased to 11% of the gross national product and is largely a result of physician efforts to decrease LOS.

Role of Physician Volume

The factors that impact outcome can be divided into two major components: physician and hospital. The physician component includes not only the technical ability of the surgeon but also the operative indication and preoperative health of the patient. Hospital-related issues range from hospital demographics and system efficiency to the skill of ancillary services. This study examines both physician and hospital volume as a proxy for these components. It is hypothesized that a spectrum exists for all vascular procedures. In certain operations, such as ruptured abdominal aortic aneurysm (which requires rapid access to the operating suite), the system component or hospital volume may be the most important determinant of outcome. In other operations, such as carotid endarterectomy, surgical technique may be the primary determinant of outcome.

For the mature, elective operation, physician volume is demonstrated to be an important outcome determinant. High-volume physicians have a mortality and postoperative stroke rate that is 50% less than their low-volume colleagues. It is surprising to demonstrate such a significant reduction in mortality rate as a function of physician volume because the mortality rate after CE is very low. Furthermore hospital costs were significantly less for HVPs. Those physicians that perform more CEs have significantly reduced mean LOS, thereby reducing the cost of hospitalization to society. This phenomenon is found in all patients, regardless of complexity.

These findings argue for the concentration of patients undergoing CE into the hands of HVPs. The data suggest that physician CE volume should exceed nine procedures a year to minimize both deaths and cost. The trend toward regionalized care is apparent in this data, suggesting that referring physicians are triaging more patients to both HVPs and hospitals. Although concentration of CE patients into high-volume 'regional practices' is at the expense of patient geographic and social convenience, both patient and payor outcome is improved. Consequently it is in the best interest of both the patient and payor to encourage regionalization, and physicians can expect this trend to continue.

Strengths and Limitations

The large patient population, representing all CE in a geographic area, the availability of cost data, and analysis of provider productivity from the dual perspective of patient and payor provide the unique perspective of this study. Because all CEs performed by all surgeons in a given area over a 10-year period were examined, sufficiently large patient numbers (11,199) allow resolution of the issue of morbidity rate and mortality rate in CE. Previous clinical research[13,14] reports outcome only by the physicians interested in CE. In contrast this study examined results of CE from the entire spectrum of surgical experience. From a policy perspective, this methodology provides a more stringent test of the operative risk than the analysis of selected experiences.

An additional strength of the study design is the definition of a subgroup of complex patients. Pre-existing condition influence on provider volume, clinical outcome, LOS, and cost affords a comprehensive examination of outcome from the perspective of both patient and payor. The lack of PEC effect on CE mortality was expected. We showed previously[15] that the effect of PEC on mortality in trauma patients is dependent on the magnitude of the injury and the patient's physiologic reserve.[16] Carotid endarterectomy, unlike aortic reconstruction, for example, exerts relatively little metabolic demand on the patient, thus minimizing the PEC effect on mortality. The presence of PECs does, however, clearly increase the intensity of service provided to the patient.

Limitations of the study are acknowledged. This is a retrospective examination based on hospital discharge abstract data. Analysis is necessarily limited to in-hospital outcome, as longitudinal follow-up is unavailable. Thus definition of long-term stroke-free survival, impact on quality of life, and the creation of a true cost-benefit equation cannot be addressed.

The severity of individual PECs is not distinguishable by ICD-9-CM methodology, nor is the preoperative indication for surgical intervention. These factors inhibit further patient stratification by risk or complexity and are a recognized limitation of all studies based on hospital discharge abstract data. In addition our definition of postoperative stroke includes codes for both 'occlusion of cerebral arteries' and 'central nervous system complications resulting from procedure.'[9] The increased incidence of stroke over time may be a result of variations in operative indications or improved documentation of transient postoperative neurologic deficits.

Finally the study is limited by the standard population-based concerns addressed by Jencks and colleagues,[17] who suggest there is potential under-reporting of pre-existing disease or complications in patients with life-threatening conditions. Truncation of PEC and stroke data may occur when multiple acute conditions or complications take coding precedence. In this population, 75% of patients had four or fewer of the five available diagnosis fields used. It is, however, reasonable to assume that some under reporting of PECs exists and only those PECs severe enough to warrant documentation in the medical record are being identified. Thus estimates of the PEC effect on outcome may still be conservative.

In summary CE is an operation performed by a large number of surgeons with a variable yearly volume. Both patient and payor outcome is improved by concentrating CE patients in the hands of high-volume surgeons. While this trend is already evolving, the pace of this evolution can be expected to increase as payors recognize that regionalization of certain procedures lowers costs.

Conclusions

1. Carotid endarterectomy has a mortality rate of 2.1% and stroke rate of 3.7% over the decade in this population study.
2. Mortality rate decreased while postoperative stroke rate increased.
3. High-volume physicians significantly reduce mortality, postoperative stroke rate, and cost for patients undergoing CE, independent of patient complexity.
4. Payors can be expected to concentrate CE in the hands of HVPs.

The outcome criteria of this study include not only morbidity rate and mortality rate but costs. All providers need to realize that the resources for patient care are, and will continue to be, limited. We must take the initiative in the search for solutions.

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DISCUSSIONS

DR. MALCOLM O. PERRY (Nashville, Tennessee): This is an important study by Dr. Edwards and his associates and certainly a commendable effort. It is something that needs to be done and it's not very palatable to talk about regionalization among those of us who like to be independent in our activities. But it is something that we may all have to swallow, palatable or not.

The authors and I share some concerns regarding the data. As Bill pointed out, ICDM codes are, unfortunately, not very accurate and they do not portray what really happens. The one used here, for example, used intracranial thrombectomy as part of that code, a procedure we rarely do. In addition, at least a widespread practice in the hospitals that I have been into is for the administrative clerks to change the coding on the discharge sheet. Even though we might fill it out on the floor, they will take a position that is financially better for the hospital, if it is legal to do so. So it's not uncommon for the codes to be changed.

I wonder, Bill, if there was some effort to authenticate or verify that these were accurate?

Bill pointed out that only in-hospital complications were there, and so we don't know what happened to patients later. But perhaps that could be addressed in a separate study.

The costs now in this 10-year study are probably not realistic. Most of the diagnostic studies for cerebral-vascular disease are not invasive; they're done on an out-patient basis. So these figures probably are not current.

It's interesting that the mortality and the stroke rates were not affected by the hospital volume, pointing out, once again, I think, what Dr. Edwards was saying, that what continues to be the most important factor in this particular operation is the physician.

However, when one looks at it by outcome by physician volume, I wonder how you would develop the criteria for this stratification into three groups, high, middle, and low. Was this done by priority or did the figures generate the stratification? Both of these have a statistical connotation on outcome. One is self-serving and the other, of course, may be informative.

The other thing in the analysis. You only analyzed high volume compared to low. I would think that most vascular surgeons doing carotid surgery are between 12 and 50 and not between 50 and 100 or 200, and probably not less than 10. I would think the figure is generally in the middle. I would be interested in what the statistical figures show of high compared to middle, which is probably the larger population.

The other disturbing thing in the manuscript—I noticed that you noticed it, too, Bill—was despite the fact that your figures show that the patients are going to regional centers now for their care, that is, high-volume regional centers, and yet in the latest compilation of the last 2 years of the study, the stroke rate increased rather than decreased.

Is this a statistical aberration or is this something we should worry about?

It is a Herculean effort to take statistics like this and attempt to glean important information. But it is a study that we need to do and I thank Dr. Edwards and Dr. Morris for doing so.

DR. ROBERT RHODES (Jackson, Mississippi): If I understood the slides correctly, it appears that more than half of the carotid endarterectomies are performed by low-volume physicians. And I suspect that if we looked at other diagnoses and procedures throughout this country, we would find that most of the medical care is, in fact, delivered by low-volume physicians.

Regionalization of care for many diagnoses and procedures probably could be shown to have similar benefits. This creates an interesting dilemma. A regionalized system for all such medical problems would be impractical and is not likely to be desirable. To implement such a system we probably would have to give some priority to certain disease processes. This priority might be based on an affliction's loss of productivity to society or its cost to payors. In either case, regionalization would have great implications for medical care in our society and is not likely to answer all the problems.

I would like to ask Dr. Edwards, first, is it correct that more than half the cases were performed by the low-volume surgeons? And, second, what should our priorities be in terms of assigning diagnoses and/or operations to regionalized centers? Also, who should make those decisions?

DR. WILLIAM EDWARDS (Closing discussion): Dr. Rhodes' and Dr. Perry's comments allow me to show this last slide, which shows that 40% of the carotid endarterectomies were performed by surgeons who performed nine or fewer operations. The divisions were decided before any of the data were accumulated.

After the data accumulation, this slide was generated, showing that at about nine—this is by physician volume—the mortality rate has decreased fairly precipitously and then leveled off. The cost also decreased and then leveled off.

Dr. Perry raised many of the issues concerning the use of a data base such as this: the limitations, the ICD-9 codes, and who has put these diagnoses on this discharge data. As he says this can be altered by recording clerks. They certainly can, because DRGs try to maximize payments to hospitals. I think we have our record room clerks come to us with 'May we add such and such codes to these, since this apparently was present in the patient's conditions?' These are all problems when abstract data such as this is used.

The physician expertise would appear to be important in the declining mortality rate.

In the hands of high-volume physicians, the mortality rate and stroke rate is lower when compared to low-volume physicians. Now when compared to the mid-volume, which is the 13 to 49 range, there was not that difference. There was a difference but certainly not as high.

There was another question you asked concerning cost. Cost has changed during this period. And at least from the large data base that this was generated from, it would appear as if with decreased length of stay, as we all know, as a result of DRGs, but that as high-volume physicians are assuming more and more of the carotid endarterectomies, it would appear that those patients are discharged from the hospital at an earlier time; consequently lower length of stay and consequently less cost. There was an additional shorter length of stay in the intensive care units, also leading to decreased cost.

Some of my friends asked me about my presentation of data like this. And in all due respect to Dr. Morris, this is his model. And, unfortunately, he could not be here to discuss some of this.

True Ablation of Atheromatous Plaques with Laser Energy

A Phase I Safety Study

M. KATHLEEN REILLY, PH.D., M.D.,* MALCOLM O. PERRY, M.D.,* and LILLIAN B. NANNEY, PH.D.†

A laser system coupling pulsed dye laser to a 2-mm fiberoptic catheter with incorporated angioscope has been developed for recanalization of occluded arteries. Nine patients with superficial femoral artery occlusions of 4.5 to 49 cm in length were operated on and the recanalized artery harvested for pathologic examination. There were two arterial perforations. The ease of recanalization was determined by plaque composition. Heavily calcified and yellow fibro-fatty lesions were rapidly removed. Smooth white fibrous lesions resisted laser ablation. Direct angioscopy often disclosed discontinuous areas of occlusion that were more susceptible to recanalization. These were not seen on preoperative arteriograms. Microscopic examination of the specimens showed a central core of ablation. There was no evidence of acute damage to the vessel wall, with intact internal elastic lamina demonstrated in the recanalized segments. It appears that fibrous lesions will require a different laser for ablation; however the delivery/angioscope systems function satisfactorily.

THE USE OF laser energy to ablate atherosclerotic plaque in peripheral arteries has limited application. Although several different lasers have been shown *in vitro* to remove plaque, the major limiting factor in human clinical work has been lack of an adequate catheter delivery system. The mechanism initially consisted of a bare fiber coupled to either an Argon or neodymium-yttrium-aluminum-garnet (Nd:YAG) laser. Use of these lasers was associated with unacceptably high perforation rates.[1] Subsequently a metal cap was placed over the laser fiber; this reduced the perforation rate, but thermal damage to the normal vessel still occurred.[2] In addition 'hot tip' probe technology requires the concomitant use of transluminal balloon dilation to create an acceptable channel in the artery. The excimer laser has demonstrated an ability to ablate plaque, but this is also limited by the requirement for balloon dilation.[3] Furthermore it is difficult to deliver the most effective laser wavelengths through these catheters because the fibers cannot withstand the energy pulses.[4]

Pulsed dye lasers that demonstrate a preferential absorption of the laser energy by the atheromatous plaque have been constructed. The ideal catheter delivery system should incorporate a guidance and aiming mechanism to locate and ablate exclusively the plaque. This study reports the results of a phase I safety trial of a pulsed dye laser coupled to an angioscopically guided catheter.

Methods

The laser chosen for the phase I safety protocol is a pulsed dye laser at 480 nanometers (Dye-Med Inc., Marlboro, MA). The laser is coupled to a 2-mm fiberoptic catheter with an incorporated angioscope (Medilase Inc., Minneapolis, MN). The parameters of the pulsed dye laser include a wavelength of 480 nm in the blue visible spectrum. The repetition rate can be varied between 1 and 5 cycles per second (Hz). The pulse width is 100 microseconds. The energy level ranges from 80 to 150 millijoules (mJ) at the tip of the catheter. The laser requires no special alterations to the operating room because it can be operated from a dedicated single-phase 220-V line, and it is water cooled. The Coumarin 480 dye is easy to handle, nontoxic, and there are no toxic gases produced by the laser. The 2-mm catheter includes three ports consisting of the angioscope, the laser fiber, and an irrigating channel. Figure 1 shows the catheter tip. This catheter can be adapted for use with multiple laser energy sources, and fluoroscopy is not necessary. A total of 10 limbs in nine patients were operated on after obtaining informed consent according to the FDA protocol and the Institutional

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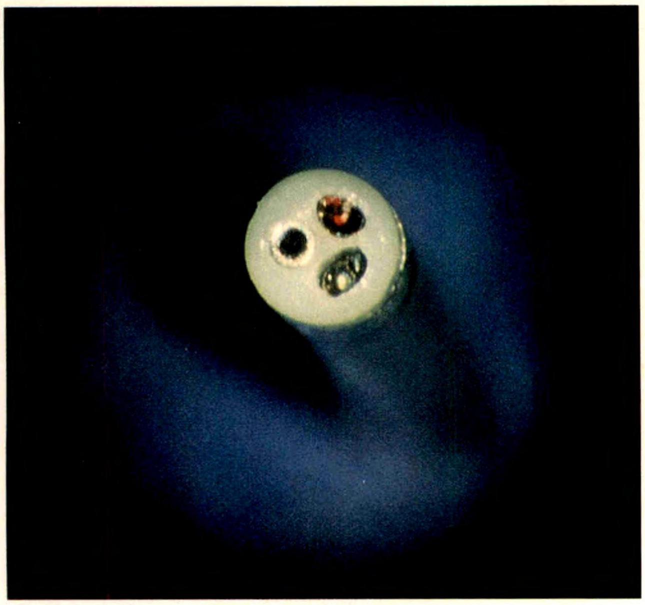

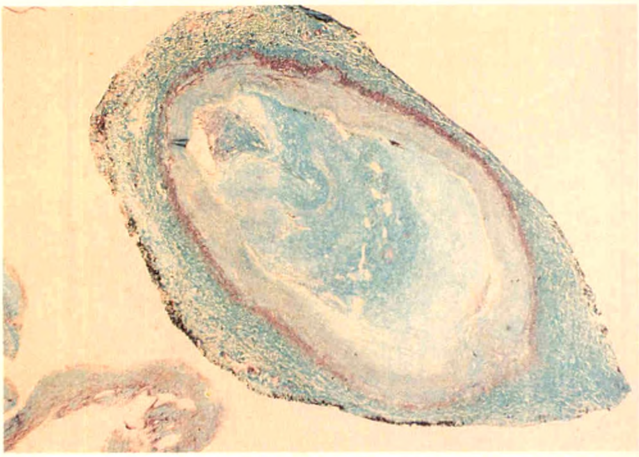

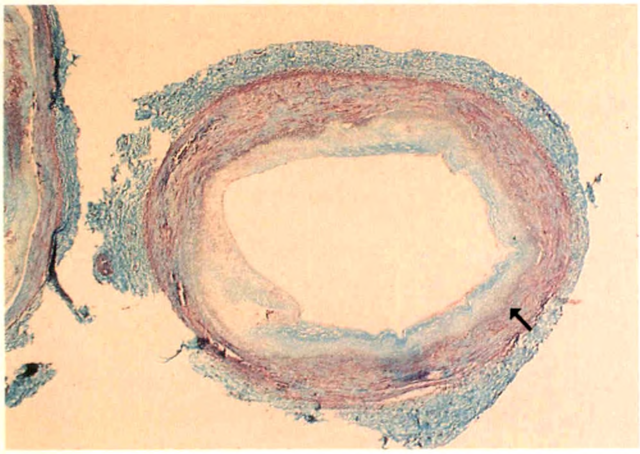

FIG. 1. Medilase catheter tip. The catheter contains three channels, including the laser fiber seen at the top right, illumination and imaging bundle seen at the bottom right, and the irrigation port seen to the left. **FIG. 2.** Occluded superficial femoral artery at the adductor canal from patient 2 (Gomori's Trichrome, ×4). The photomicrograph section shows typical total obliteration of the lumen of the artery with white fibrous plaque. **FIG. 3.** Laser recanalized segment of superficial femoral artery from patient 5 (Gomori's Trichrome, ×4). The photomicrograph shows the central core of recanalization surrounded by a thin rim of residual plaque. Note the intact internal elastic lamina (arrow).

Review Board. All patients had superficial femoral artery occlusions of 4.5 to 49 cm in length. Each patient had standard preoperative evaluation, including noninvasive vascular laboratory studies as well as arteriography. Eight of the nine patients had progressive claudication over a 6- to 9-month period that failed to respond to standard medical management. One patient presented with rest pain and gangrene of two toes in the right foot. Table 1 outlines the risk factors for peripheral vascular disease that were present among these nine patients.

Operative Technique

The common femoral, superficial femoral, and profunda femoral arteries were exposed through standard groin incisions. The catheter was then connected to the laser by a sterile, flexible coupling cable. The cable for the sterile imaging bundle was connected to the catheter. The irrigation port was continuously flushed with heparinized saline at 250 mmHg. The patient was given systemic heparin (100 U/kg) and a vascular clamp placed across the common femoral artery. An arteriotomy was made in the common femoral artery. The Medilase catheter (Medilase Inc., Minneapolis, MN) was then introduced through the arteriotomy, and advanced to the level of obstruction under direct angioscopic control. After inspection of the area of occlusion, the laser was set to deliver between 80 and 100 mJ of energy for calcified or fatty plaque, and 120 to 150 mJ for smooth white fibrous plaque. The laser was then activated as gentle forward pressure was applied to the catheter to hold it against the plaque. After 20 to 30 pulses, the area was inspected through the angioscope, and the laser energy adjusted based on the appearance of the crater created. After the laser had opened a channel through the lesion, the catheter was withdrawn slightly and by a combination of rotation and external compression, it was angled to enlarge the lumen. After the lesion was completely traversed by the laser, an intraoperative

TABLE 1. *Risk Factors for Peripheral Vascular Disease*

Risk Factor	Number of Patients*
Diabetes	0
Hyperlipidemia	4
Tobacco use	8
Hypertension	7
Alcohol abuse	5
Cerebrovascular disease	2

* Multiple risk factors were present in some patients.

arteriogram was obtained. The laser-treated segment of artery was harvested for pathologic examination, and the patient then had a standard femoral-popliteal bypass using either reversed saphenous veins or 6-mm polytetra-fluoroethylene grafts.

Results

Table 2 shows a comparison of the arteriographic and angioscopic appearance of the superficial femoral artery occlusions in these nine patients. There are several observations that are apparent. The first is the inadequacy of the preoperative arteriogram in predicting the success or failure of laser recanalization of the artery. In the two instances where smooth continuous white fibrous plaque was observed angioscopically, there was no evident effect of the laser in removing this plaque, regardless of the length of the occlusion. In one instance where a continuous occlusion was observed to consist of complex fatty and calcified plaque, total recanalization of the artery occurred. This lesion, however, was a short segment total occlusion of only 5 cm. In the remaining five limbs, where discontinuous plaques were observed, varying lengths of recanalization was accomplished, ranging from 14.5 cm to 32 cm. It appears from these results that the length of the occlusion *per se* was not a good predictor of success. Rather a discontinuous series of short occlusions or the presence of a complex, fatty, and calcified plaque were the findings associated with successful recanalization. In each instance where the total length of occlusion could not be recanalized, microscopic examination of the artery at this point demonstrated the occurrence of predominantly white fibrous plaque. Figure 2 shows the microscopic appearance of such a lesion from patient 2 at 28 cm from the origin of the superficial femoral artery, where the catheter could no longer be advanced. This photomicrograph shows the typical appearance of smooth white fibrous plaque totally occluding the lumen of the artery. There is no evidence of recanalization by the laser at this point. Figure 3 is a section taken from the midportion of the recanalized artery harvested from patient 5. This demonstrates a recanalized central core with a thin rim of residual plaque. Acutely there is no evidence of damage to the artery, and the internal elastic lamina remains intact.

The complications occurring in these nine patients consisted of two instances of perforation of the artery. One was mechanical and occurred on insertion of the catheter. The second was a perforation occurring when the laser was discharged in the presence of thrombus adherent to the wall of the artery. No distal embolization of debris was observed in this study. Furthermore no evidence of dissection of the arterial wall was observed.

Discussion

In the past few years there has been an intense interest in endovascular techniques for treating atheromatous arterial disease. Balloon dilatation is the most widely used method, but it can be applied to less than a third of patients presenting with arterial stenoses in the extremities.[5] Although the controlled expansion balloon developed by Gruntzig and Hopff[6] causes less damage than the coaxial method originally proposed by Dotter and Judkins,[7] arterial injury occurs each time. Intimal flaps and dissections are almost always formed, and attenuation of the wall with occasional disruption has been reported.[8] Even if initial patency is obtained, the trauma to the vessel wall

TABLE 2. *Comparison of Arteriographic and Angioscopic Appearance of Superficial Femoral Artery Occlusions*

	Arteriographic Appearance			
Patient	Location	Length of Occlusion (cm)	Angioscopic Appearance	Length of Recanalized Segment (cm)
1	Mid SFA	12.5	Continuous white fibrous plaque	0
2	Total SFA	46.5	Discontinuous complex plaque	28.0
3	SFA 7 cm distal to origin	49.0	No image*	0
4	Total SFA	24.5	Continuous white fibrous plaque	0
5	Mid SFA	5.0	Continuous complex plaque	5.0
6	Total SFA	41.5	Discontinuous complex plaque	15.0
7	Total SFA	25.0	Discontinuous complex plaque	14.5
8	Mid SFA-R	16.0	No image*	0
	Total SFA-L	23.5	Discontinuous complex plaque	23.5
9	Total SFA	33.0	Discontinuous complex plaque	32.0

* No image was obtained due to the misalignment of the cable connection to the laser.

apparently incites the development of neointimal hyperplasia, which leads to a significant restenosis rate, often requiring additional dilations, or surgical reconstruction.[9]

Recent technological advances permit various lasers to be used in attempts to obtain a smooth, less hostile luminal surface after dilatation. Moreover complete occlusions of arteries can be treated by balloon dilatation if a channel for the guidewire can be created by the laser. Attempts to deliver the laser energy through a bare fiber resulted in severe damage to the artery. The end of the fiberoptic catheter was then covered with a metal cap. This 'hot tip' laser was used to open a small channel for the guide wire and balloon.[2] As experience was gained with this method, it soon became clear that the thermal damage was extensive, and recent reports describe only 50% or less patency rates at 6 months.[10,11] Furthermore it was pointed out that the tip could be heated by radiofrequency or catalytic means rather than the expensive laser system if the heat injury problem could be overcome.[12]

A new method using computer control of the laser has been developed. Often called the 'smart laser,'[11] visible laser light is used to induce fluorescence in the atheromatous plaque.[13] The patterns of fluorescence are analyzed by computer and the laser energy delivered only when a plaque is identified. Despite the attractive theory, the overlap in fluorescence patterns precludes absolute separation of plaque from normal arterial wall. Thus successful reopening of diseased vessels without wall damage is not often achieved. Even when it works, adjunctive balloon dilatation is required to obtain a satisfactory lumen.[14]

Newer fiberoptics permit the application of lasers that previously could not be used because of absorption by and damage to the delivery fiber. Photochemical dissolution of molecular bonds leading to plaque ablation is possible with some of these lasers. The excimer laser has been tested in this area, and a recent report describes successful reopening of 77% of the diseased superficial femoral arteries treated, but again balloon dilatation was needed to enlarge the channel.[4] The early results are disappointing because of a 29% restenosis rate within 9 months.

These rather somber reports have raised the question of whether the endovascular techniques are already doomed.[15] The intense marketing effort that fueled the widespread use of the 'hot tip' laser, and its poor results, have led to a great deal of pessimism regarding this methodology. It is clear that basic research must be completed before additional devices are put into general use.

The primary objective of a phase I safety study is to assess the potential for harm of a new method. The design of this study requires a careful pathologic examination of the treated arteries; therefore only acute changes can be evaluated. The mechanical perforation seen in this study was clearly related to catheter manipulation, but the other one was caused by the laser. This perforation underlined one of the problems with the system: it is difficult angioscopically to determine the depth of a laser-produced crater. The principal limitation of the angioscope is its inability to assess the depth of penetration of the plaque within the arterial wall, as it can only visualize the surface of the lesion. Three-dimensional anatomy is not easily seen either directly or on the video screen. As shown by examination of specially stained sections of the treated femoral arteries, the arterial wall was not otherwise damaged. This is one of the 'cold' lasers, and no heat injury was expected, but photochemical reactions can occur, and these might not be seen on the fresh specimen. Longer-term follow-up, perhaps with pathologic samples for examination, will be needed to assess late results. The additional question of whether this laser system will, similar to balloon dilation, incite the development of neointimal hyperplasia, can be answered only by longitudinal studies.

Most of the endovascular methods of plaque removal have created only a small opening, usually 2 to 3 mm in diameter. This clearly is insufficient, and thus balloon dilation has been necessary to enlarge the channel. The laser used in the current study is capable of removing most of the plaque, but the configuration of the catheter tip directs the beam straight ahead. An angled tip is needed, with rotational properties, to permit the beam to be applied to the entire circumference of the lesion. In conjunction with the new tip, intraluminal ultrasound probes can be used to obtain an image of the arterial wall layers, and the newly created channel.[16] This promises to be more helpful than direct angioscopy in evaluating the opening, and in directing the laser energy to the plaque.

The laser can readily ablate the usual calcified atheromatous plaque, but the smooth white fibrous lesion is resistant to ablation by laser energy levels at 480 nm. This is most likely due to the absence of color in the surface of the lesion, decreasing the amount of laser energy absorbed. The level of energy approved by the FDA for this study is modest, and perhaps an increase in millijoules and exposure time would be sufficient. Using the intraluminal ultrasound probes, the beam could be safely applied only to the plaque. In reality the laser could be changed if need be; the heart of the method is the catheter delivery system, and the suggested modifications should solve some of the current problems.

The discontinuous configuration of atheromatous disease of the superficial femoral artery renders it more susceptible to plaque removal. A long, predominantly fibrous lesion clearly would be more of a problem than a series of short obstructions, whereas a series of discontinuous occlusions was associated with a greater likelihood of successful recanalization. Preoperative arteriography was not useful in predicting the success of recanalization, as it was unable to distinguish between patients with continuous occlusions *versus* those patients who had multiple discrete segmental occlusions. This feature is perhaps one of the reasons why complete mechanical endarterectomy of the artery can be difficult to obtain. The endarterectomy devices may skip over the thinner, relatively normal segment of artery, thus creating a shelf of diseased intima that possibly could lead to local thrombosis. Laser ablation of the plaques should not cause these changes. In fact, the pathologic studies of treated arteries reported herein showed a smooth, clear luminal surface without flaps or dissections.

The numerous reports of failure surrounding laser-assisted balloon dilation of arteries was not unexpected. It was already clear that balloon dilation caused extensive vessel damage, and most attempts to treat lesions longer than 10 cm are unsuccessful.[17] The 'hot tip' laser was deployed prematurely, without a careful scientific evaluation, and thermal injury was predictable. The weak hope that 'heat glazing' of the arterial wall would somehow improve the flow surface and resist platelet aggregation and thrombosis has not been realized.[18,19] These discouraging results do not imply that all endovascular methods are now to be abandoned, but they do emphasize that carefully designed and executed laboratory and clinical studies are required before these methods are adopted as standards of care.[20]

It is necessary that all patients entered with an 'intention to treat' be included in the long-term follow-up. It is not acceptable to discard those in whom initial 'technical success' is not obtained. Life-table methods of evaluation are needed, and objective means of follow-up, based on physiologic and anatomic data, are required if a realistic assessment of the procedure is to be made. The phase II efficacy study now beginning is designed to answer some of these questions.

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DISCUSSIONS

DR. ROBERT SMITH (Atlanta, Georgia): As Dr. Perry rightly emphasized, safety and long-term results are equally as important as immediate success in revascularization techniques. Too little attention has been paid to this concept during the initial wave of enthusiasm to apply laser therapy to atherosclerotic occlusive lesions, resulting in the present mood of pessimism concerning this modality.

At Emory we have had limited experience with the percutaneously introduced Eximer laser to create a channel for balloon angioplasty in infrainguinal occlusions. The results have been somewhat disappointing, which is in line with that reported in the literature.

Our interventional cardiologists, however, have had a much larger experience with the Eximer laser, treating 100 patients with coronary atherosclerosis, primarily to enlarge the lumen through long stenotic lesions sufficiently to permit balloon dilatation. They have had two perforations, one of which required urgent operation. Acute arterial dissections and late restenosis are significant problems that continue in their experience as well.

I have several questions for the authors. Using their angioscope, can the operator observe while the laser energy is actually applied? Or does the focal length of your scope permit only intermittent viewing during treatment?

Will your anticipated refinements allow more precise steering and aiming of the laser beam? In your phase I study you attempted to create a lumen in several segmental occlusions more than 40 cm long. Even with more sophisticated techniques for true laser ablation, do you not expect that greater success will occur with the shorter lesions over time?

And, finally, do we really have to achieve the same long-term patency with endovascular techniques as with surgical bypass grafting to show efficacy? If the laser method can be improved to the point that it could be repeated periodically with little morbidity but the desired overall clinical effect, would that not be an acceptable alternative, particularly in poor risk patients?

DR. JIM SEEGAR (Gainesville, Florida): I also wish to compliment Dr. Perry on his excellent presentation and thank him for providing me with his manuscript to review.

What you have seen is a phase I trial, as we have seen with many laser systems that previously were and now are being used. This system is unique in that it provides angioscopic guidance along with a pulse dye laser system.

I agree with two of the conclusions that Dr. Perry presented, including, first, that angiography is inadequate to characterize the lesion to be treated by an endovascular technique as opposed to a bypass technique. And, second, that the composition of the treated lesion is of critical importance in these kinds of technologies.

However the question must be raised as to whether this new system is truly better than the systems that are currently on the market or approaches the ideal laser delivery system that we would all like to see.

This ideal laser delivery system would allow precise delivery of laser energy, probably using multiple different wavelengths to areas of occluding atherosclerotic plaque and thrombus or providing a very accurate assessment of our ability to differentiate occluding plaque from normal arterial walls.

This system uses angioscopy for plaque discrimination and laser aiming. While you clearly can aim the laser with the angioscope, it has been our experience with angioscopy, as indicated by Dr. Perry, that it is very difficult to distinguish the arterial wall from the atherosclerotic plaque at times and to determine when you have actually passed through the arterial wall.

The pulse dye laser probably is an inadequate laser for recanalization. This laser in this study was able to recanalize thrombotic occlusions and probably fatty plaque but not fibrotic occlusions. And this would mean that it would act pretty much like all the other systems available now.

Finally it is important that we recognize that phase I trials are often misleading. In our initial phase I trial of the Argon laser and the hybrid probe, we were able to show that we had perforation in only two of nine patients, that angioscopy appeared to be an adequate guidance system, that minimal wall injury and minimal debris were produced, and that recanalized lesions appeared adequate for improved distal flow. All of that clearly was not correct.

I have four questions for Dr. Perry. The first is — and I think he partially answered this, but I would like him to elaborate on it a bit. The angioscopic identification of calcified plaque, was that compared to microscopic observations? How do we know that what was not being recanalized in this study was not merely thrombotic occlusions that could have, in reality, probably been recanalized with thrombolysis?

Second, was any effort made to reperfuse these vessels to determine luminal thrombogenecity?

In contradistinction to what Dr. Perry said, *in vitro* data would suggest that pulse lasers are actually more thrombogenic than the continuous wave lasers.

Third, can this system be used percutaneously? Our experience has been that our intraoperative attempts have had a significantly lower success rate than percutaneous procedures, and disturbingly, that when intraoperative attempts were made and failure occurred, we saw an increased incidence of complication with immediate bypasses. Did any of these patients have problems with their bypasses after this phase I trial?

And, finally, can this system be used to create an adequate channel? A 2- to 4-mm channel probably is not adequate in a 6-mm vessel for improved distal flow.

DR. MALCOLM O. PERRY (Closing discussion): In regard to the question about the angioscope, we have to turn it off when the laser is on, so it is intermittent, and that is one of the problems. The steering is very poor; it requires a lot of manipulation, and that accounts for some of the eccentricity of the core sample and, the inability to create a proper channel. The angled tip and the ultrasound probe, we hope, will enable us to apply the energy properly.

I agree wholeheartedly that in poor-risk patients this technique has a place *versus* surgery. It looks to me, though, that we will have to accumulate a large number of patients to determine that, and it will be a few years in the future.

There was premature deployment of some of these other systems before they had been adequately tested in the long term, and we certainly would not want to make that mistake. It may have a place in poor-risk patients.

We have looked at it only during operation and harvested the specimen.

Dr. Seegar, of course, you are an expert in this business, which I am not. Multiple wavelengths are important, and that might be the answer to the problem with the fibrous plaque. It is white and glistening compared to a chromophore, for example, and the ability to handle it.

As I mentioned earlier, Dr. Reilly is exploring the possibility of using a solid-state laser rather than the Cumarand at 480 nm that we are now using. That plus the increased power might do it. It is an inadequate laser for this. I think our studies have documented that.

We do know about the pathologic condition in those vessels because the plaque was incompletely removed in each instance. All of these were pathologically examined after the specimens removed; therefore we know what happened to them. We can not comment on the thrombogenesis because all the specimens were harvested. That will be part of the phase II efficacy study.

Of more concern to me at the outset was this problem with inciting of neointimal hyperplasia that seems to occur after all of these intraluminal ablations.

None of the patients had a problem with bypass. Dr. Reilly treated them all; all had a bypass, and they all worked. A 2-mm channel clearly is not adequate. We wanted to avoid the problem with balloon dilation, and we think we need to ablate all or most all of the plaque if this is going to work.

Evolution of Renal Insufficiency in Ischemic Nephropathy

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TIMOTHY E. CRAVEN, M.S.P.H.,† and JOHN F. REDDING II, B.S.*

This retrospective review of data collected during a recent 42-month period from 58 consecutive patients with ischemic nephropathy submitted to operative management in the authors' center was undertaken to report the rate of decline in their renal function during the period before intervention and to examine the impact of operation on their outcome. Based on serum creatinine values, immediate preoperative estimated glomerular filtration rates (EGFR) ranged from 0 to 46 mL/minute (mean, 23.85 ± 9.76 mL/minute). Eight patients were dialysis dependent or anuric at the time of operation. Patients with at least three sequential measurements for calculations of EGFR changes during the 6 months before operation ($n = 50$) and the first 12 months after operation ($n = 32$) were used to describe the preoperative rate of decline in EGFR and the impact of operation on this decrease in the operative survivors. In addition comparative analyses of data from patients with unilateral *versus* bilateral lesions and patients classified as having improvement in EGFR *versus* no improvement after operation were performed. Comparison of the immediate preoperative EGFR with the immediate postoperative EGFR for the entire group showed significant improvement in response to operation. Likewise the rate of deterioration in EGFR for the total group was improved after operation. A similar improvement in the rate of deterioration in EGFR was seen in the subgroup of patients who received an immediate improvement in EGFR in response to operation. These data argue that ischemic nephropathy is a rapidly progressive form of renal insufficiency. Although individual responses to operation were heterogeneous, renal revascularization may provide both immediate improvement in renal function and an improvement in its rate of deterioration during follow-up in patients with ischemic nephropathy.

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OCCLUSIVE DISEASE OF the renal artery may produce two pathologic sequelae. Through increased stimulation of the renin–angiotensin system, such lesions may secondarily lead to the production of renovascular hypertension (RVH). Separately severe occlusive disease may lead to inadequate effective renal plasma flow and diminish excretory function of the kidney. Traditionally study of the sequelae of renovascular occlusive disease has centered on the pathophysiology and management of the resultant renovascular hypertension. Recent reports, however, have emphasized the potential for simultaneous retrieval of excretory function in some patients with combined hypertension and renal insufficiency.[1-3] These observations have renewed awareness of this functional consequence of renal ischemia and have led to the coinage of the term *ischemic nephropathy.* By definition, ischemic nephropathy reflects the presence of anatomically severe occlusive disease of the extraparenchymal renal artery in a patient with excretory renal insufficiency.

Enthusiasm for the role of renal revascularization in patients with ischemic nephropathy has led some surgeons to use empiric correction of renovascular occlusive disease using the unproven hypothesis that such correction might prevent the subsequent loss of excretory renal function. Such an approach implies that ischemic nephropathy is a progressive form of renal insufficiency and that renal revascularization will have a salutary impact on its natural history. Unfortunately little information is available in the literature from which such a premise can be argued.

This retrospective review of data collected during a recent 42-month period from patients with ischemic nephropathy submitted to operative management in our center was undertaken to describe the demography of such patients, to report the rate of decline in their renal function during the period before intervention, and to examine the impact of renal revascularization on these changes.

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Demography of Patient Population

During the period from January 1, 1987 through June 30, 1990, 178 patients were submitted to elective operation for renovascular occlusive disease at the Wake Forest University Medical Center by the authors of this article. The subgroup of 58 patients with ischemic nephropathy who had at least moderate azotemia and serum creatinine of not less than 1.8 mg/dL at the time of operation constitutes the population evaluated in this report. There were 30 men and 28 women. Ages ranged from 22 years to 79 years (mean, 63 years; median, 64 years). Age distribution by decade is shown in Figure 1. Race distribution included 54 whites, 3 blacks, and 1 East Indian. Hypertension was present in all patients and ranged in duration from 6 months to 30 years. Only 12 patients (21%) had been hypertensive for less than 5 years. Highest known blood pressures in the group ranged from 180/100 mmHg to 250/140 mmHg. Drug regimens used for control of hypertension before operation ranged from two to six agents. Eight patients had diabetes mellitus (14%), and 48 patients (83%) had a history of cigarette abuse.

Fifty-one patients (88%) manifested one or more of the following clinical features of extrarenal site-specific atherosclerotic damage: cardiac disease (86%), cerebrovascular disease (36%), and peripheral vascular disease (26%). Seventeen patients (29%) had required one or more hospitalizations for treatment of decompensated congestive heart failure with acute pulmonary edema during the year before operation.

Materials and Methods

Entry into the group reported in this article required that the patient have a serum creatinine value of at least 1.8 mg/dL at the time of operation in the absence of potential nephrotoxic agents (*e.g.*, angiographic contrast material, angiotensin-converting enzyme inhibitors, or high-dose diuretics) and after correction of dehydration.

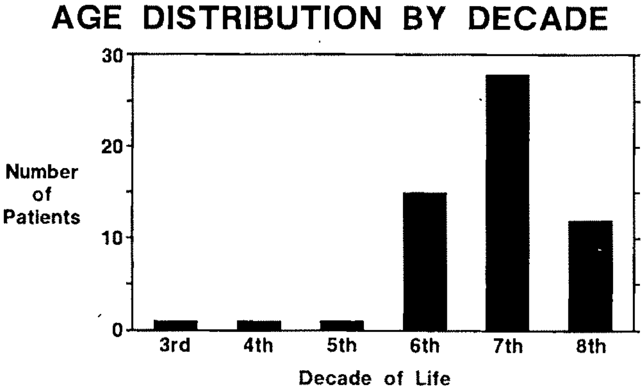

FIG. 1. Graphic depiction of the age distribution of patients with ischemic nephropathy included in the report.

TABLE 1. *Preoperative EGFR Values*

EGFR Value (mL/min)	Number of Patients	%
40–49	2	3
30–39	7	12
20–29	29	50
10–19	9	16
Dialysis and EGFR < 10	11	19

EGFR Estimated glomerular filtration rate

Serum creatinines at operation ranged from 1.8 to 15.3 mg/dL. In addition to the immediately preoperative serum creatinine value, all measurements of serum creatinine obtained during the 6-month period before operation and for the period between 1 week and 1 year after operation were registered in the database for analysis in this study.

Data Management

For purposes of this study, all serum creatinine values were transferred to a calculated measure of estimated glomerular filtration rate (EGFR) by integrating the patient's sex, age, weight, and body surface area (BSA), using the formula of Cockroft and Gault[4] adjusted for body surface area[5] as follows:

Estimated glomerular filtration rate = (140 − age) (weight)/(72)(serum creatinine) × 1.73/BSA, where BSA was calculated using the following formula: BSA = (Height) (0.725 cm) × (Weight) (0.425 kg) × 0.0007184. Finally the EGFR values for female patients were multiplied by 0.85 to correct for an average lower rate of creatinine synthesis in females.

Using this methodology EGFR values immediately before operation ranged from 0 to 46.0 mL/minute (mean, 23.85 mL/minute). Seven patients were dialysis dependent for 6 to 54 days before operation. One additional patient became anuric 12 hours before surgery. Table 1 summarizes the immediate preoperative EGFR values by severity grouping.

Statistical methods. Descriptive statistics (*e.g.*, means, standard deviations, and so on, of continuous data, and frequencies and relative frequencies of categoric data) were computed, and the data were examined to verify that assumptions of statistical tests were met. Postoperative survival rate was estimated using the product-limit method.[6] The EGFR was calculated from serum creatinine measurements as described earlier. The natural logarithm transformation of EGFR was analyzed. A linear regression model was used to estimate the rate of deterioration of the natural log of EGFR separately for the 6 months before and 12 months after surgery. Mean slope was estimated by a weighted average of the individual slopes, using the inverse of their estimated variances as weights. Only subjects with at least three preoperative or at least three postoperative serum creatinine measurements with the appropriate time intervals were used to estimate the preoperative and postoperative slopes. Mean percentage changes in EGFR during the preoperative and postoperative periods for groups of patients were calculated using the following formula: mean percentage per week decrease = $100 \times (1\text{-}e^{\text{mean slope}})$.

Paired t tests were used to test the significance of the initial increase in renal function, estimated as the difference between the last preoperative and first postoperative EGFRs. An analysis of 26 subjects with both preoperative and postoperative slopes demonstrated that the slopes were not correlated within subject ($r = 0.0927$, $p = 0.6525$); therefore unpaired t tests were used to test for significant differences between preoperative and postoperative slopes. Tests for significant differences in mean slopes by improvement status and lesion site were performed using unpaired t tests.

In addition to data available from the 58 patients submitted to elective operation, data from three remaining patients with ischemic nephropathy were included in calculations of the preoperative rates of deterioration of EGFR. Two of these patients were evaluated at our center, but they were not treated by the authors. The remaining patient was treated by emergency operation for total renal artery thrombosis after an attempted percutaneous transluminal angioplasty.

Definitions

Blood pressure response to surgery. Blood pressure and antihypertensive medication requirements at a point at least 8 weeks after operation were used for analysis of hypertensive response to operation. *Cure* was defined as a diastolic blood pressure less than or equal to 95 mmHg on no antihypertensive therapy. Patients were considered *improved* if they met the criteria of the following algorithm: (1) if diastolic pressure was controlled (≤ 95 mmHg) before surgery, medication requirements to achieve control must have been significantly reduced (equivalent of a reduction of two drugs); (2) for those patients whose blood pressures were not controlled before surgery and a drop in diastolic pressure of less than 20 mmHg was associated with postoperative control, medication requirements must have been reduced by at least the equivalent of one drug; (3) achievement of control with a drop in diastolic blood pressure of at least 20 mmHg on no more medications than were used before surgery. Patients not meeting these criteria for classification as cured or improved were categorized as *failed.*

Renal function response to surgery. A clinically significant change in global excretory renal function was characterized as a change in EGFR by at least 20%. Estimated glomerular filtration rate values obtained at least 1 week after operation were used for classification. Patients were categorized as *improved* if they were no longer dependent on dialysis or if an increase in EGFR of at least 20% was realized. Patients were considered *worsened* if there was a decrease in EGFR of 20% or more or if the institution of dialysis was required. All others were considered to have had *no change* (± 19% change).

Patient Management

Preoperative Evaluation

In addition to a complete medical history, physical examination, and resting electrocardiography, 37 patients underwent further cardiac evaluation. These evaluations included resting echocardiography (27 patients), exercise echocardiographic or electrocardiographic stress testing (17 patients), and coronary arteriography (18 patients). Cardiac reserve was assessed before operation in three patients by overnight pulmonary artery cannulation with measurements of cardiac performance during volume loading. Coronary arteriography results showed at least moderate coronary artery atherosclerosis in all patients studied. This led to preliminary coronary artery bypass grafting in three patients. Table 2 summarizes cardiac risk factors for operation identified from both clinical assessment and diagnostic evaluation.

Renal arteriography was performed by the Seldinger technique and iohexol (Omnipaque,® Winthrop Pharmaceuticals, New York, NY) by use of either conventional arteriography (56 patients) or intra-arterial digital subtraction arteriography (two patients). Significant renal artery disease (≥80% area reduction) was present unilaterally in 20 patients (6 occlusions; 14 severe stenosis: 12 ostial, 2 nonostial). Five of these patients had severe disease of the renal artery to a solitary kidney. Significant bilateral disease was present in 38 patients (31 occlusions; 45 severe stenoses: 44 ostial, 1 nonostial). Renal artery disease was caused by atherosclerosis in all but three patients. These remaining three patients had fibromuscular dysplasia.

TABLE 2. *Summary of Cardiac Risk Factors*

Factor	Number of Patients	%
Clinical history		
Angina pectoris	22	38
Congestive heart failure	19	33
Coronary artery bypass	5	9
Electrocardiogram		
Left ventricular hypertrophy	43	74
Strain pattern	5	9
Prior myocardial infarction	23	40
Arrythmias	10	17
Abnormal echocardiography	2	3
Abnormal stress test	5	9
Positive coronary arteriogram	18	31
At least one factor present	49	85

Four patients had undergone previous nephrectomy, and one patient had a congenitally absent contralateral kidney. An associated abdominal aortic aneurysm was present in 15 patients, and severe occlusive aortoiliac disease was present in 27 patients.

Twenty patients were evaluated with renal vein renin assays. Lateralization (ratio more than 1.5 to 1.0) of renin activity was found in 7 of 14 patients with unilateral lesions and in 4 of 6 patients with bilateral lesions. Split renal function studies were performed in only six patients. Although the tests demonstrated reduced excretory function in the involved kidneys, they were interpreted as being positive using our previously reported criteria[7] in only three patients.

Operative Treatment

Before the operative procedure was begun, all patients had pulmonary artery catheters inserted and radial arteries cannulated for continuous monitoring of hemodynamic parameters during the perioperative period. Other routine components of our operative management for renal procedures have been detailed elsewhere.[8]

Ninety-six kidneys underwent operation. Nineteen patients underwent unilateral renal artery repair. Thirty-four patients underwent bilateral repair, and four patients had unilateral repair with contralateral nephrectomy of a nonfunctioning kidney with a nonreconstructible artery. One patient was treated with primary nephrectomy only. No patient undergoing unilateral repair had uncorrected significant contralateral renal artery disease. Renal revascularization was accomplished by aortorenal bypass grafting in 45 instances. Autogenous saphenous vein was used in 32 of these, and expanded polytetrafluoro-ethylene grafts were used for 13 reconstructions. Renal artery reimplantation was used for four vessels, and thromboendarterectomy was used in 42 vessels. Seventeen patients underwent simultaneous aortic reconstruction for correction of abdominal aortic aneurysm (11 patients) or severe aortic occlusive disease (six patients). Among these simultaneous aortic procedures, 6 patients had unilateral renal artery repair, 10 patients had bilateral repair, and 1 patient had unilateral repair with contralateral nephrectomy.

TABLE 3. *Operative Mortalities*

Age (yrs)	Preoperative EGFR ml/min	Procedure	Cause of Death
68	20.5	Bilat. revasc. + AAA	Postoperative bleeding
69	32.3	Bilat. revasc.	Pneumonia, MSOF
69	23.2	Unilat. revasc. + AAA	CVA
72	9.5	Unilat. revasc. + AAA	CVA, renal failure
76	23.6	Bilat. revasc.	Pneumonia, MSOF

Bilat., bilateral; revasc., renal revascularization; unilat., unilateral; AAA, abdominal aortic aneursym; MSOF, multiple system organ failure; CVA, cerebrovascular accident.

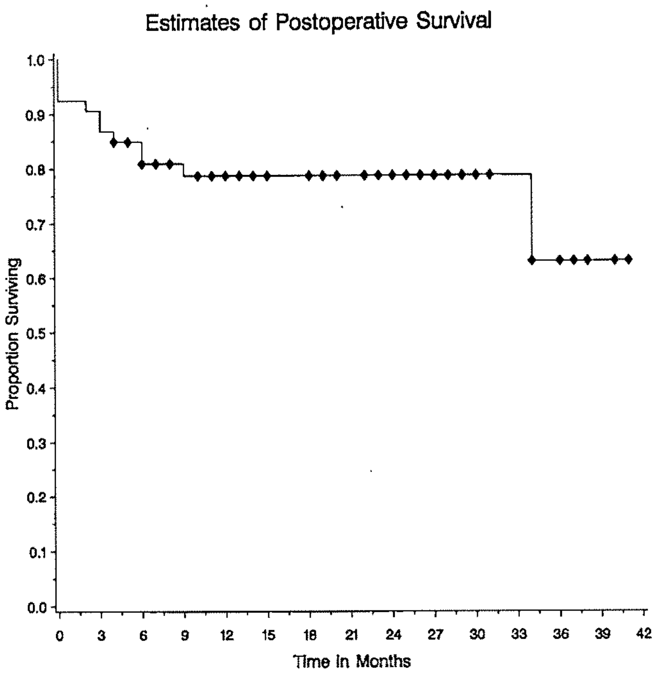

FIG. 2. Kaplan–Meir life table analysis of survival for the patients included in the report.

Results of Operation

Postoperative Morbidity and Mortality Rates

Early events. Five patients died in the early postoperative period and are considered operative mortalities. These deaths produced an overall operative mortality rate of 9%. Table 3 summarizes the pertinent clinical data in these patients.

Major nonfatal postoperative morbidities that significantly prolonged hospital stay occurred in 12 patients. These were prolonged ileus (1), congestive heart failure (2), myocardial infarction (1), arrhythmia requiring pacemaker insertion (2), respiratory failure requiring prolonged intubation (1), pneumonia (3), pedal cholesterol embolization (1), pseudomembranous colitis (1), ascites requiring peritoneal-venous shunt insertion (1), and activation of peptic ulcer disease (1). In addition one operative survivor who was dialysis independent before operation required initiation of chronic renal dialysis in the immediate postoperative period. The immediate preoperative EGFR value in this patient was 7.1 mL/minute.

Late events. Follow-up ranged from 2 to 41 months (mean, 19.8 months). Seven of the 53 patients (11%) who survived operation have required initiation of chronic

TABLE 4. *Blood Pressure Response to Operation*

Response	Number of Patients	%
Cured	8	15
Improved	41	77
Failed	4	8

TABLE 5. *Renal Function Response to Operation*

Change in EGFR	Number of Patients	%
Improved (≥20%↑)	31	59
No change (±19%)	15	28
Worse (≥20%↓)	7	13

renal dialysis for treatment of progressive deterioration in renal function at 1 week to 36 months after operation. Three of these patients had received initial improvement in EGFR by operation. The other morbid event requiring repeat hospitalization during the follow-up period for management of a renal related problem was thrombosis of bilateral renal artery bypass grafts in one patient at 10 weeks after operation (both were corrected by reoperation).

There were nine deaths during the late follow-up period. These occurred at 2 to 34 months after operation. Each of these deaths was from a cardiovascular origin. Survival after operation for the entire group is summarized in Figure 2 using Kaplan–Meier life-table analysis. Four of the nine patients who died (44%) during follow-up were dialysis dependent at the time of death. Similarly four of the nine patients (44%) who became or remained dialysis dependent after operation have died.

Blood Pressure Response

Using the aforementioned criteria for classification, Table 4 summarizes the blood pressure response in the 53 patients who survived operation. Eight patients (15%) were cured of hypertension, 41 patients (77%) received significant improvement in the severity of hypertension, and four patients (8%) received no benefit and were classified as failures.

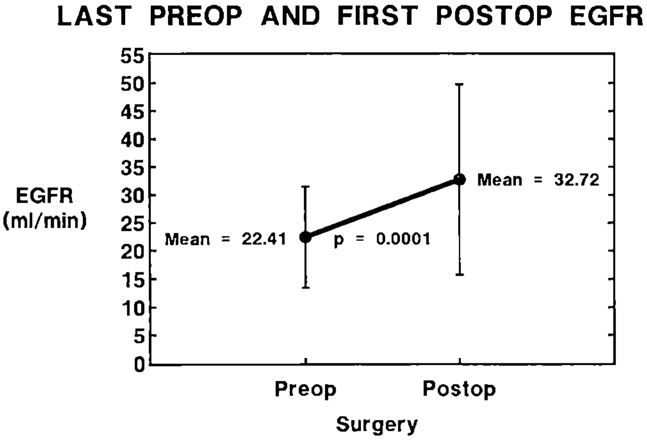

FIG. 3. Comparison of the mean EGFR immediately before and at least 1 week after operation. The p value for the differences is determined using t test for unpaired data.

Renal Function Response

Immediate effect on EGFR. Figure 3 compares the preoperative mean EGFR value (22.41 ± 9.71 mL/minute) with the immediate postoperative mean EGFR value (32.72 ± 17.54 mL/minute) for the entire group of operative survivors. As depicted in the figure, this increase in the mean EGFR value was significant (p = 0.0001) when analyzed using the t test for paired data. Table 5 classifies the operative survivor's renal function response using the aforementioned criteria for determination of response. Using this method, 31 patients (59%) received improvement in EGFR. No significant change in EGFR was noted in 15 patients (28%), and seven patients (13%) had a significant drop in the EGFR immediately after operation.

The immediate impact of operation on EGFR when examined according to the site of disease and operation is summarized in Table 6. In this evaluation, lesions (and procedures) to solitary kidneys and procedures consisting of unilateral revascularization with contralateral nephrectomy are recorded with the bilateral group. As noted in Table 6, when the groups were evaluated by site of operation, the bilateral group experienced a significant improvement in EGFR after operation (p = 0.0001). Although four patients (33%) in the unilateral group received an improvement in EGFR (≥20% EGFR increase) after operation (Table 7), no statistically significant benefit was seen when all unilateral disease patients were collectively evaluated (Table 6).

Finally the effect of operation on each of the preoperatively dialysis-dependent/anuric patients is summarized

TABLE 6. *EGFR (ml/min) Response* Versus *Site of Operation**

		Preoperative			Postoperative		
Operation	N†	Mean EGFR		SD	Mean EGFR		SD
Unilateral	12	25.94	±	11.86	29.14	±	14.34
		p = 0.1633					
Bilateral	41	21.38	±	8.89	33.77	±	18.39
		p = 0.0001					

* p values are for paired t test.

† Operative deaths and preoperatively dialysis-dependent patients are excluded from the analysis.

TABLE 7. *Change in EGFR* Versus *Site of Disease*

	Unilateral		Bilateral	
Change	N	%	N	%
Improved (≥20% increase)	4	33	27	66
No change (±19% change)	7	58	9	22
Worse (≥20% decrease)	1	9	5	12
Total	12		41	

TABLE 9. *Change in the Natural Log of EGFR/Week*

	Total Group			
	N	Mean Slope		SD
Before operation	50	−0.0330	±	0.0742
		p = 0.0462*		
After operation	32	−0.0094	±	0.0291

* p values are for unpaired t test.

in Table 8. As noted, six of these eight patients were rendered dialysis independent by operation.

Evaluation of rate of change in EGFR. Tables 9 and 10 summarize the analyses of rates of deterioration in EGFR for both the preoperative and postoperative periods of study. These data are presented as the rate of change of the natural log of EGFR per week. The preoperative rate of decline was significantly greater than the postoperative rate of decline in the analysis of the entire group (p = 0.0462) (Table 9) and in the analysis of the improved subgroup (p = 0.0226) (Table 10). In contrast, the similar comparison of the preoperative and postoperative rates of change for the unimproved group (Table 10) showed an insignificant increase (p = 0.2551) in its slope after operation.

A graphic presentation of the antilog of these data that depict the percent change in EGFR/week for the total group and the respective subgroups of improved and unimproved patients are shown in Figures 4, 5, and 6. The immediate impact of operation in these respective groups is also depicted in these figures.

The rate of change in natural log of EGFR before operation and after operation, when analyzed by site of disease (unilateral *versus* bilateral), is summarized in Table 11. Although improvement is noted in the mean value, no statistically significant difference was found in the unilateral group when the preoperative slopes (−0.0325 ± 0.0606) and postoperative slopes (−0.0105 ± 0.0244) of the natural log of change in EGFR/week were compared (p = 0.2757). A greater improvement in the rate of deterioration in EGFR after operation was observed in the bilateral group (preoperative: −0.0357 ± 0.0838 *versus* postoperative: −0.0092 ± 0.0304). Nevertheless these changes also were not statistically significant (p = 0.0798).

Discussion

Little information is available in the literature that accurately describes the incidence, prevalence, spectrum of clinical presentations, or the natural history of ischemic nephropathy. Nevertheless, circumstantial evidence suggests that it may be a more common cause of progressive renal failure in the atherosclerotic age group than previously recognized. In a 1986 survey, 73% of end-stage renal disease (ESRD) patients were in the atherosclerotic age range (more than 40 years old), and the median age was greater than 60 years.[9] Likewise more than 50% of nondiabetic patients with ESRD have hypertensive nephropathy as their presumed diagnosis.[10] In a report by Mailloux et al.,[11] a presumed renal vascular cause of ESRD increased in frequency from 6.7% for the period 1978 to 1981 to a frequency of 16.5% for the period 1982 to 1985. The median age at onset of ESRD for that group was the oldest of all groups, falling in the seventh decade of life. Each of these clinical characteristics is in concert with

TABLE 8. *Results in Dialysis-dependent Group*

Age (yrs)	Sex	Dialysis Duration	Immediate Postoperative EGFR	Site of Operation
51	F	11 days	32.7	Bilateral
63	M	32 days	34.6	Bilateral
65	M	6 days	44.5	Bilateral
59	M	30 days	49.0	Bilateral
76	M	10 days	30.7	Bilateral
61	F	0*	13.5	Bilateral
66	M	6 days	CD†	Unilateral
75	M	54 days	CD†	Unilateral

* Patient had developed anuria; operation undertaken without dialysis.
† CD, continued on dialysis.

TABLE 10. *Change in the Natural Log of EGFR/Week* Versus *EGFR Response to Operation*

	Improved Group			Unimproved Group		
	N	Mean Slope	SD	N	Mean Slope	SD
Before operation	23	−0.0547 ±	0.1029	18	−0.0045 ±	0.0152
		p = 0.0444				
		p = 0.0226			p = 0.2551	
After operation	24	−0.0048 ±	0.0098	8	−0.0144 ±	0.0241
		p = 0.5978				

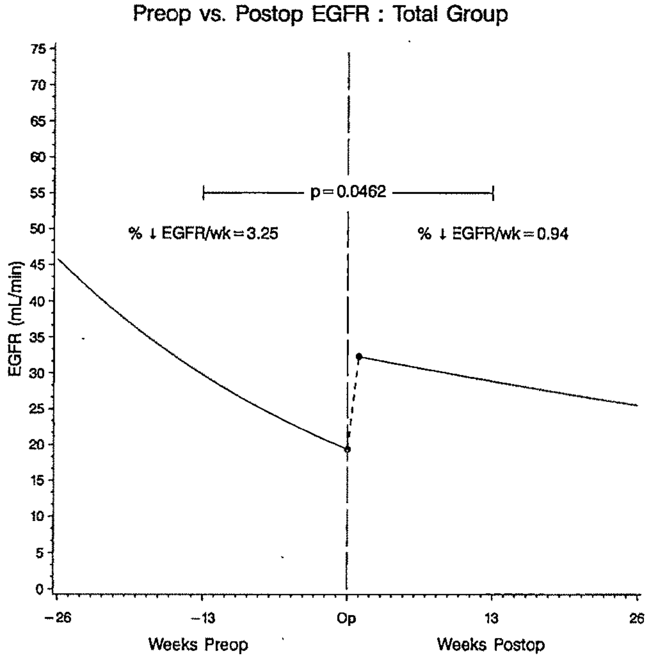

FIG. 4. Graphic depiction of the percentage deterioration of EGFR per week for the entire group during the 6 months before (n = 50) and after (n = 32) operation. The immediate effect of operation on EGFR is also depicted. The p values for differences are determined using t test for unpaired data. Note the improvement in the slope of decline in EGFR after operation.

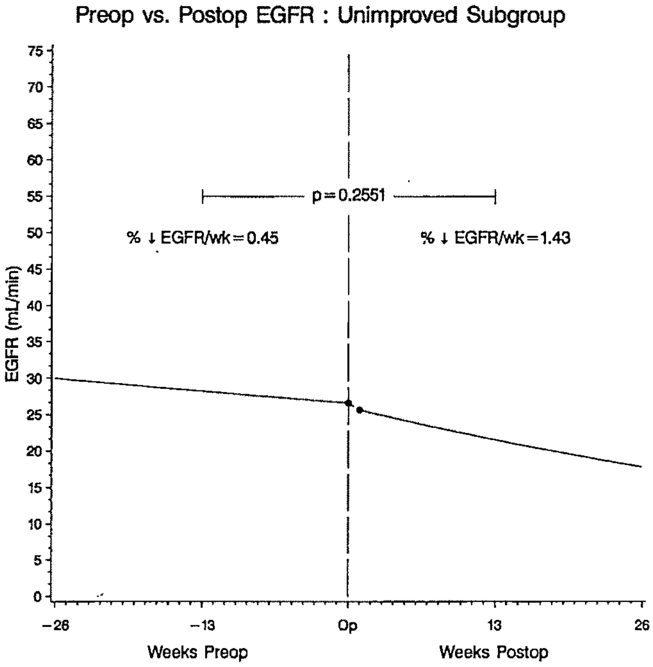

FIG. 6. Graphic depiction of the percentage deterioration of EGFR per week during the 6 months before (n = 18) and after (n = 8) operation in the group of patients who received no significant immediate benefit in EGFR after operation. The p values for differences are determined using t tests for unpaired data. Note the absence of improvement in the rate of deterioration of EGFR following operation in this group.

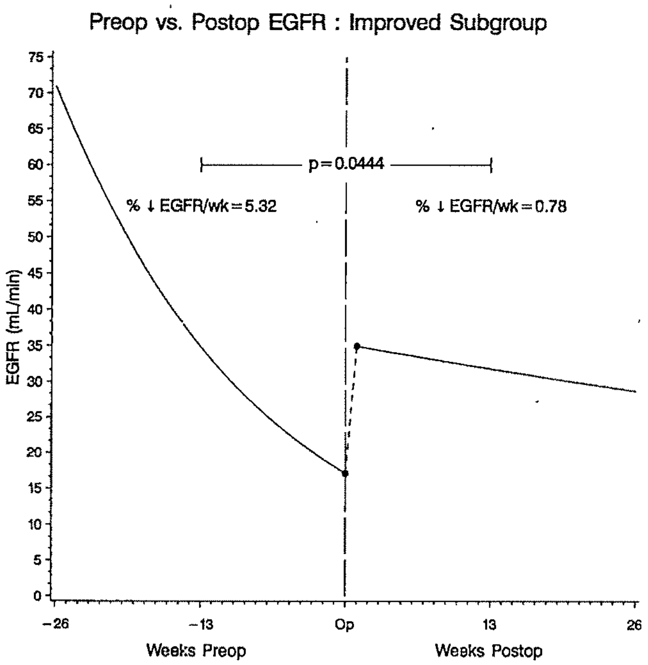

FIG. 5. Graphic depiction of the percentage deterioration of EGFR per week during the 6 months before (n = 23) and after (n = 25) operation in the group of patients who received at least a 20% improvement in EGFR following operation. The immediate effect of operation on EGFR in this group is also depicted. The p values for differences are determined using t test for unpaired data. Note the improvement in the slope of decline in EGFR after operation in this group.

the demographic data of our patient group with proved ischemic nephropathy. In our group all patients had at least moderate hypertension, the mean age was 63 years, and only 14% had diabetes mellitus. We believe these data argue that renovascular disease may be either the primary cause or a superimposed secondary accelerant of renal insufficiency in a larger proportion of patients with renal insufficiency than commonly recognized. Using this premise as a guide, we currently screen all adult patients over the age of 50 years who have newly recognized renal insufficiency when hypertension of any level is a coexistent morbidity.

TABLE 11. *Change in the Natural Log of EGFR/Week* Versus *Lesion Site**

	Unilateral			Bilateral		
	N	Mean Slope	SD	N	Mean Slope	SD
Before operation	14	−0.0325 ±	0.0606	36	−0.0357 ±	0.0838
		p = 0.2757	p = 0.8994		p = 0.0798	
After operation	7	−0.0105 ±	0.0244	25	−0.0092 ±	0.0304
			p = 0.9235			

* p values are for unpaired t test.

Renal duplex sonography is our preferred method for this preliminary screening. Our experience with the use of renal duplex sonography as a screening technique has been previously reported.[12] In that review we found renal duplex sonography to have an overall accuracy of 96% for establishing the presence or absence of main renal artery occlusive disease. Because the term *ischemic nephropathy* implies the presence of global renal ischemia, we think it is an adequate method to initially screen the renal insufficiency patient when performed by an experienced technician. Through preliminary screening with renal duplex sonography, we limit the use of arteriography in renal insufficiency patients to those with either positive renal duplex sonography or severe hypertension.

Our predominate reliance on standard 'cut film' arteriography in patients with renal insufficiency requires comment. In our experience adequate assessment of the renal vasculature and juxtarenal aorta requires multiple injections when intra-arterial digital subtraction angiography is used. The use of a single midstream flush aortogram requires no more contrast material than that required for such multiple intra-arterial digital subtraction studies. In addition standard arteriography provides information concerning cortical thickness and renal length as well as improved clarity for interpretation of the renal artery anatomy. The fact that arteriography in such patients with severe renal insufficiency, especially those with concomitant diabetes mellitus, can aggravate renal failure is widely recognized. Nevertheless, we believe this risk is justified in such patients who have severe or accelerated hypertension and in patients with a positive renal duplex sonogram. In these circumstances the potential benefit derived from identification and correction of a functionally significant renovascular occlusive lesion exceeds the risk of arteriography.

The primary aim of this retrospective review is to examine the rate of deterioration of renal function in a group of patients with ischemic nephropathy and to evaluate the impact of renal revascularization on subsequent changes. Although we believe this analysis provides valuable data to address these issues, there are several biases inherent in this study that may affect the power of these observations. Because we evaluated the rate of deterioration of EFGR before intervention by retrospectively collecting the preoperative data from a group of patients who already had been submitted to operation, we created patient selection bias for inclusion in the study. Because referral of the patients was predominately dependent on the presence of either severe hypertension, accelerated hypertension, new onset renal insufficiency, or accelerating renal insufficiency, the patient group probably is weighted toward the later stages of the clinical syndrome of ischemic nephropathy. Because patients predominantly entered our series because of clinical sequelae of their disease, it is inappropriate to infer that our data are representative of the entire population of patients with ischemic nephropathy. Therefore, the prevalence and duration of a preliminary clinically silent phase remains unknown.

The second issue potentially introducing error is the methodology used for calculating changes in renal function. Because the study is a retrospective evaluation of data, the number of serum creatinine values and the intervals between their collection amongst the respective patients are heterogeneous. Furthermore the use of indirect methods such as serum creatinine levels to estimate GFR has been debated widely.[5,13,14] Rolin and his associates[5] performed a study comparing measured GFR values using labeled iothalamate against EGFR using modifications of the Cockcroft and Gault formula.[4] In their study, EGFR as used by us had a 0.932 correlation with measured GFR values. Clearly measurement of GFR by the iothalamate clearance method is a superior method for determining renal function. Nevertheless use of the EGFR values can provide a valuable approximation of actual GFR when applied to values obtained from an entire group of patients.

Although the rate of change of EGFR before intervention is probably affected by selection bias, it is extremely rapid. This is even more pronounced when it is compared with the rate of decline of EGFR from other causes of renal insufficiency. In the preliminary data used to make sample size calculations for the initiation or the Modification of Diet in Renal Disease,[15] the rate of decline in GFR was estimated to be approximately 0.5 mL/min/month for renal insufficiency patients on a standard diet. Noteworthy is the fact that patients with known renovascular occlusive disease were excluded from entry into that database. With the rate of deterioration suggested in that pilot data, it would require approximately 40 months for the GFR to drop from 40 mL/min to 20 mL/min. In contrast using the rate of decline in our entire group for comparison, less than 5 months would be required for a patient with ischemic nephropathy to experience a similar level of deterioration.

Retrospective comparison of the rate of deterioration in EGFR before operation for the group who received improvement in EGFR by operation *versus* those receiving no benefit suggests that the rate of decline in GFR may have value in predicting the probability of retrieval of GFR by operation. Unfortunately the heterogenicity of individual slopes of change in EGFR prevent comment on a critical rate of decline that would predict retrieval of renal function by operation. Nevertheless a rapidly deteriorating GFR should alert the physician to the potential presence of ischemic nephropathy and should argue for the likelihood of retrieval of function by operation when ischemic nephropathy is identified.

Renal revascularization had a beneficial impact on both the rate of decline in EGFR, as well as the EGFR itself, when data for the entire group are analyzed collectively. Nevertheless as a group the salutary effect of operation on the rate of deterioration was only seen in the subset that experienced an immediate improvement in EGFR by operation. This observation may have major clinical significance, for the detrimental effect of renovascular occlusive disease theoretically may be from either of two causes. First, the lesion may limit renal perfusion to a degree that it affects excretory function. Second, it may be the source of microscopic atheroembolization, which destroys functioning renal parenchyma. Our data suggest that correction of lesions causing reversible ischemia will provide both an immediate improvement in EGFR as well as a slowing of its rate of decline when compared with the preoperative rate of decline. Unfortunately when the lesion was not producing significant reversible ischemia as reflected by the absence of improvement in EGFR immediately after operation, no improvement in the rate of decline in EGFR was realized after operation. This argues that when atheroembolism is the only potentially active pathophysiologic consequence of the lesion, its correction does not lead to clinically important slowing of the rate of deterioration in renal function.

Comparison of the effect of correction of unilateral and bilateral lesions reasserts our earlier observations regarding predictors of retrieval of renal functions.[16] Specifically we again observe that patients with bilateral lesions or lesions to solitary kidneys have the highest likelihood for retrieval of significant renal function after operation. Although there was an improvement in the mean slope of decline in EGFR after operation in both the unilateral and bilateral subgroups, this change did not reach statistical significance in either group. Because statistically significant improvement in the rate of deterioration was seen when all slopes were analyzed collectively (Table 9), this absence of significance in the subgroup analysis is probably related to small sample sizes.

We found significant improvement of EGFR after operation in an important minority (33%) of patients treated for unilateral lesions. This adds to our enthusiasm for the merits of operative treatment of unilateral lesions in the renal insufficiency population, especially when functional proof of the presence of RVH can be obtained from renal vein renin assays or split renal function studies. Because uncontrolled hypertension can be an important independent cause of both progressive renal insufficiency and an accelerator of cardiovascular morbid and mortal events, we believe that operative treatment of such patients is justified even without regard to the issue of retrieval of renal function. In this regard the importance of the blood pressure response to operation seen in the majority of patients (92%) can not be overemphasized. At least a portion of the beneficial impact of operation on the rate of decline in EGFR may have been a consequence of improved blood pressure control and removal of high-dose antihypertensive medications.

This report of our experience underscores the rapidity of deterioration of renal function in patients with ischemic nephropathy and demonstrates the potential benefit of operation on both GFR and its rate of deterioration in a subset of patients. Nevertheless the risk associated with operation is not inconsequential and requires comment. Certainly the patients included in this report are at accelerated risk for any major operative procedure. All patients had some degree of renal insufficiency, and 88% had cardiac, cerebrovascular, or peripheral vascular manifestations of atherosclerosis. With such evidence of multifaceted, site-specific end-organ damage in this relatively elderly population, one must question the merits of benefit afforded by a therapy that has a 9% operative mortality rate and a cumulative 1-year survival rate of only 78%. Nevertheless one must place this risk and rate of survival into context with the probability of survival without operation. In a study of the duration of survival after institution of dialysis, Mailloux and coworkers[11] found that end-stage renal disease caused by uncorrected renovascular disease was associated with the most rapid rate of death during follow-up. In their study patients with renovascular disease had a median survival after initiation of dialysis of only 27 months and a 5-year survival of only 12%. This equates to a death rate in excess of 20% per year. The life-table survival curve of our group of patients with ischemic nephropathy suggests that if an individual survives operation and the early follow-up period, he or she is afforded an improved probability of survival. Even when operative deaths are included, the probability for 2- and 3-year survival appears to be significantly better than that seen in patients who had not received intervention and had progressed to the point of dialysis dependence.

The data presented in this retrospective review argue that ischemic nephropathy is a rapidly progressive form of renal insufficiency. The effect of renal revascularization on renal function, however, was heterogeneous. Nevertheless the frequency of both retrieval of renal function and slowing of the rate of its deterioration during follow-up was gratifying and encourages enthusiasm for the continued study of the role of operation in properly selected patients. Most importantly the results argue that a carefully controlled prospective randomized trial comparing operation with medical therapy is necessary to confirm the value of operation in patients with controlled hypertension. Only through this method could one accurately clarify the role of operation in the prolongation of the period of dialysis independence and long-term survival in patients with ischemic nephropathy.

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DISCUSSION

DR. CALVIN ERNST (Detroit, Michigan): Dr. Dean's manuscript is so detailed and contains so many valuable data that time does not permit comprehensive discussion of the entire study. Consequently I will focus on that portion dealing with renal revascularization and concomitant aortic reconstruction.

The 17.6% operative mortality rate for combining a renal revascularization and aortic reconstruction reported in the manuscript underscores the principle that such procedures should not be used indiscriminately. Therefore it is important to know the natural history of arteriosclerotic renal arterial stenosis before embarking on simultaneous repairs.

Clearly mere presence of a renal artery stenosis in a patient undergoing aortic reconstruction does not mandate renal revascularization. In an attempt to identify those arteriosclerotic renal arterial stenoses that progress to occlusion, at the Henry Ford Hospital we retrospectively studied 66 arteriosclerotic renal arteries in 48 patients, followed by 194 sequential arteriograms during an average interval of 4.5 years.

All 48 patients had undergone aortic reconstruction and all had renal arterial stenoses that were not repaired at the time of aortic reconstruction. By annual follow-up arteriography, the natural history of these lesions were studied. We found that 7 or 10.6% of the stenoses progressed to occlusion and presumably deterioration of renal function, although this was by no means proved. And those most likely to occlude were narrowed by 80% or more. No lesions or stenoses less than 60% on the preceding aortogram progressed to occlusion in the subsequent study.

Furthermore multiple risk factors, including change in serum creatinine, did not correlate with renal arterial occlusion.

It remains unclear then what effect renal arterial occlusions may have on patient survival or renal function. Intuitively it seems that preservation of renal parenchymal tissue by renal revascularization among patients undergoing aortic reconstruction is beneficial. But only if the operative risk is minimal and can be justified by prevention of renal failure, which may require dialysis.

Therefore, with Dr. Dean's large experience in this excellent study, I would like to ask three questions. First, what are your indications for concomitant renal revascularization and aortic reconstruction?

Second, could you identify any clinical markers in the eight patients who were on preoperative dialysis, such as progression of the renal arterial stenosis, and thereby predict which patients may develop this potentially preventable complication?

And, third, what is the effect of a unilateral stenosis on renal function, exclusive of the hypertensive damage to the contralateral unprotected kidney? Can we expect renal revascularization to improve renal function under such circumstances?

DR. GERALD LAWRIE (Houston, Texas): We looked at a group of 80 patients with creatinines greater than 2 from a series of more than 1000 patients or actually, in this series, 919 patients. I think the first thing to recognize is that most patients, in our experience, with severe renovascular hypertension do not have renal insufficiency.

These patients looked fairly similar to what Richard presented. And about 40% of our patients had bilateral disease. When we came to look at predictors of response in terms of improvement of renal function and lack of response, we had a lot of trouble coming up with any clinical or laboratory or angiographic predictor that would tell us which patients we should operate on with a view to restoring renal function.

Obviously the patient with bilateral renal stenosis with good-sized kidneys who comes in and has to be put on dialysis usually is a good candidate.

But most of these patients fall into this category of creatinines around 2 to 3. When we look at the people who had a good response and the people who had a poor response after surgery, it was about a 50–50 proposition. And bilaterality did not seem to be much of a factor.

We looked at a number of other factors and were not able to determine what patient should get this treatment. Of course it is a very complicated problem because in atherosclerotic patients we see development of renal failure and in hypotensive patients we see development of renal failure.

And then in people with limitation of blood flow to the kidney we certainly see renal insufficiencies, as Richard has so elegantly demonstrated.

So the question I have for Richard is as he looks at this data in these tests, does he really have a strong feeling of confidence that he can select patients, on the basis of these tests, who will respond with a high degree of probability, that is, the nondialyzed patients?

Considering the fact these people tend to be sicker—and we've certainly documented long-term survival is much lower in people with preoperative renal insufficiency, despite renal revascularization—is it worth subjecting them to the risk of surgery, which in most cases is significant because of their multiple-system problems, unless we have a very clear-cut test that will tell us reasonably unequivocally that they will respond well in terms of renal function?

DR. RICHARD DEAN (Closing discussion): The group of patients who came off dialysis stayed off dialysis. There were, however, patients who subsequently went on dialysis who had not been on dialysis preoperatively.

This group of patients had been followed up to 42 months. One patient in that group who recurrently became dialysis dependent several months after operation had a graft thrombosis, was operated on, and again became dialysis, independent after repeat bypass.

I appreciate the discussant's comments and I will, in essence, combine Dr. Lawrie's and Dr. Ernst's questions. In the renal insufficiency group of patients, I don't think we have good predictors up to this point to accurately identify who will respond with improvement in renal function. The data that we reviewed here does give some clue, however, to a predictor. That predictor is the rate of deterioration in function before operation. For example, a patient who has a creatinine level of 2 mg/dL today who had a creatinine level of 2 mg/dL last year is unlikely to have a return of function after operation. In contrast, a patient who had a creatinine level of 1.5 mg/dL two months ago and 4 mg/dl today has a higher probability for return of function.

Unfortunately, with the heterogenicity of the data and the small numbers, there was no critical rate of deterioration below which one did not improve, above which one did improve. I think it is a general marker that those who are deteriorating rapidly have the most likelihood of return of function and equally or even potentially more important have a higher likelihood of having a decrease in their postoperative rate of deterioration.

One can look at the effect of the renal artery lesion as producing ischemia or causing hypertension. Either of these effects can cause renal insufficiency. Renal ischemia that can cause such renal insufficiency can also be caused by atheroembolism from the renal artery lesion. Although obviously present in many of these patients, atheroembolism by itself does not appear to be an independent factor that increases the rate of deterioration.

The issue of risk of operation cannot be overstated. One should place this into context, for this is a group of people who are rapidly deteriorating, and a group who will become dialysis dependent within months if left uncorrected.

Patients who have uncorrected renovascular disease and end-stage renal disease may have a 20% per year death rate. Our survival curve of our group is significantly better than that even when operative deaths are included. It's as though the stress of the operation is significant, but if one gets through the operation and receives a benefit from it, one has a significantly protected survival.

The final question that Dr. Ernst had concerns the indications for combining renal artery surgery with aortic surgery. I am somewhat simplistic about this, in that I do not believe that the patient who has even an angiographically severe lesion who does not have hypertension or renal insufficiency should undergo prophylactic renal revascularization. If they are azotemic or if they are hypertensive, then we would combine the renal artery procedure with the aortic reconstruction.

Finally, there are two reasons for potential benefit in the unilateral lesion where, obviously, one would expect to find bilateral arteriolar disease. One reason is the potential for return of function in the 'protected' kidney; I think that is a much less common phenomena than suggested by some nephrologists.

The second benefit of operation in the unilateral group is improved control of hypertension and its benefit to renal function in the long term.

In that regard, the use of preoperative predictors to identify who will have benefit in hypertension is valuable in assessing the patient with a unilateral renal artery stenosis.

Femoral-Distal Bypass with *In Situ* Greater Saphenous Vein

Long-term Results Using the Mills Valvulotome

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During a 7-year period, 440 consecutive *in situ* saphenous vein grafts originating in the groin were performed in 371 patients, exposing the entire vein for valvulotomy with a modified Mills valvulotome. Critical ischemia was the indication for bypass in 68%, and the distal anastomosis was to an infrapopliteal artery in 46%. Thirty-day operative mortality was 2.0%. Postoperative surveillance identified 18 stenotic grafts (4.1%), which were revised while still patent (primary revised patency); 36 grafts (8.2%) underwent revision after graft occlusion (secondary patency). Five-year life-table analysis showed overall primary revised patency of 78%, secondary patency of 83%, limb salvage of 88%, and patient survival of 66%. Femoroperoneal and inframalleolar bypasses fared well. The presence of diabetes did not diminish late graft patency. In contrast to reversed vein grafts, long infrapopliteal *in situ* grafts had long-term secondary patency similar to shorter femoropopliteal bypass grafts ($p > 0.05$). These results, coupled with the versatility and simplicity of the technique as used in the present series, suggest that *in situ* vein grafting is the procedure of choice for long infrapopliteal bypass.

SINCE THE FIRST femoropopliteal bypass was reported in 1949,[1] the autologous greater saphenous vein has remained the most versatile and durable conduit for revascularization below the inguinal ligament. Originally widely used in reversed fashion to accommodate the venous valves, the saphenous vein was left *in situ* by Hall[2] and others, employing various approaches to valve lysis. Because of the apparent complexity of the method, wider adoption of the *in situ* technique was limited until introduction of the modified Mills valvulotome[3] by Leather et al.[4] in 1979. Since then a number of centers have developed extensive experience with the *in situ* method of saphenous vein bypass.[5-7] Simultaneously significant advances have been made in small-vessel surgical instrumentation and technique, enhancing the success of all methods of vein bypass.[8] The optimal approach to infrainguinal autogenous revascularization remains controversial, particularly regarding the increasing numbers of surgical candidates with disease below the popliteal artery. In an effort to clarify the role of *in situ* saphenous vein bypass, the current study of a large experience from a single institution was undertaken.

Methods

In 1983 a policy of preferential use of the *in situ* greater saphenous vein for all infrainguinal arterial reconstructions was adopted on the vascular service at Brigham and Women's Hospital. Routine preoperative arteriography documented the distribution of occlusive lesions, and no infrainguinal reconstruction was undertaken in the presence of hemodynamically significant inflow disease. Preoperative venography or vein mapping with duplex ultrasound were not routinely used. At surgery, the greater saphenous vein was exposed through a single incision over a sufficient length to reach the chosen recipient artery. The distal artery was isolated in the subfascial tissue through the vein-harvesting incision in the case of the popliteal, posterior tibial, and proximal peroneal arteries. The anterior tibial and distal peroneal arteries were exposed through a counterincision over the anterior compartment, with fibulectomy to expose the peroneal, and a tunnel either through the interosseous membrane or subcutaneously over the tibia. Dorsalis pedis exposure was obtained through a vertical incision just medial to the artery with care to avoid creating a narrow skin bridge to the venous incision and a distal anastomosis directly under the pedal incision. The vein was left in continuity after exposure with protection by a pad moistened with a bal-

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anced electrolyte solution containing sodium heparin 1 U/mL and papaverine 60 mg/L. On occasions when the vein appeared to be of questionable size or quality, this solution was used to gently dilate the involved segment through a side branch.

After systemic heparinization, the saphenofemoral junction was detached with lateral suture closure of the common femoral vein. The most proximal saphenous valve was excised, and a suitable anastomosis in the femoral artery was created. On removal of occluding clamps, a modified Mills valvulotome was introduced sequentially through side branches to incise the valve leaflets, confirmed by vigorous flow through the end of the vein. In 22 grafts performed over the last year of study, angioscopy was employed to guide valvulotomy with a long-handled Mills instrument. The vein was clipped at the end and allowed to pulsate under arterial pressure while all visible venous side branches were ligated. The distal anastomosis was created using loupe magnification and 6-0 or 7-0 polypropylene suture, employing elastic vessel occluders or soft bulldog clamps for arterial control. To avoid vein kinking, infrageniculate popliteal anastomoses were usually performed after passing the vein into the popliteal space through an anatomic tunnel.[9] On completion of the graft, sterile continuous-wave Doppler and completion arteriography were routinely employed to assure adequacy of flow and absence of residual valve leaflets and arteriovenous fistulas.[10] All patients received perioperative prophylactic intravenous antibiotics. In infrapopliteal bypasses, low-molecular-weight dextran was employed at 500 mL/day for the first 48 hours after operation. Aspirin, 300 mg daily, was recommended for the indefinite postoperative period.

At regular postoperative visits, patients were assessed by history and physical examination as well as by segmental limb pressures and pulse volume recordings, supplemented by duplex ultrasound during the latter part of the series. A decrease in ankle/brachial index of greater than 0.10 between visits or a decrease in overall graft velocity to levels below 0.4 m/second were grounds for repeat arteriography to assess the status of the graft, even in the absence of symptoms. All preoperative, surgical, and postoperative data were collected prospectively on a microcomputer-based registry. Actuarial life-table analysis was employed for graft patency, limb salvage, and patient survival rates. *Primary patency* tables define as patent all grafts requiring no revision after leaving the operating room. *Primary revised patency* tables define as patent all grafts that required no revision plus grafts revised while patent by percutaneous or surgical methods. *Secondary patency* tables define as patent all unrevised grafts and grafts revised patent plus grafts that were disobliterated and revised after a single occlusion. Standard error estimates were calculated using the Greenwood method,[11] and comparisons of life-table estimates were made using the Mantel-Cox log rank test of significance.[12]

TABLE 1. *Characteristics of 371 Patients Undergoing 440 In Situ Saphenous Vein Grafts*

Characteristic	Number
Mean age (years)	68 (range, 31–91)
Male:Female	259:181
Smoking	271 (62%)
Hypertension	265 (60%)
Coronary artery disease	190 (43%)
Diabetes mellitus	168 (38%)
Chronic pulmonary disease	83 (19%)
Renal failure	23 (5%)

TABLE 2. *Location of Distal Anastomoses in 440 In Situ Saphenous Vein Grafts*

Location	Number
Popliteal above-knee	79 (18%)
Popliteal below-knee	161 (37%)
Tibioperoneal trunk	12 (3%)
Anterior tibial	46 (10%)
Posterior tibial*	79 (18%)
Peroneal	54 (12%)
Dorsalis pedis	9 (2%)

* Includes nine at inframalleolar level.

Results

A total of 440 consecutive *in situ* greater saphenous vein bypass grafts were performed in 371 patients for atherosclerotic occlusive disease between March 1983 and June 1990. The characteristics of the patient population are listed in Table 1. Coronary artery bypass had been performed in 17 patients. In 299 (68%) instances, critical limb ischemia was the indication for surgery with ischemic rest pain in 148, ulcer in 87, and gangrene in 64. Disabling claudication was the surgical indication in the remaining 141 (32%) operations. Procedures for popliteal aneurysm were excluded from analysis. In 406 (92%) instances, saphenous vein bypass was a primary reconstruction, and in the remaining 34 (8%) a previous infrainguinal revascularization had been performed. In 78 (18%) procedures inflow to the groin was previously or concurrently improved with iliac balloon angioplasty (13) or aortofemoral (14), iliofemoral/femorofemoral (14), or axillofemoral (6) bypass. The proximal anastomosis was at the groin level in all instances, and an infrapopliteal artery was the site of distal anastomosis in 200 (45%) procedures, including 18 grafts to a level below the ankle joint (Table 2).

Operative complications occurred in 104 patients (24%), including major cardiopulmonary, renal, or cerebrovascular complications in 33 (8%) (Table 3). Cardiac and wound complications were the leading causes of

TABLE 3. *Thirty-day Operative Morbidity Rate After 440* In Situ *Saphenous Vein Grafts*

Complication	Rate
Systemic	
Myocardial infarction	16 (3.6%)
Congestive heart failure	11 (2.5%)
Arrhythmia	20 (4.5%)
Renal failure*	8 (1.8%)
Pulmonary failure	8 (1.8%)
Stroke	2 (0.4%)
Transient ischemic attack	2 (0.4%)
Deep vein thrombosis	2 (0.4%)
Local	
Wound infection/seroma/hematoma	37 (8.4%)
Graft occlusion	27 (6.1%)
Reoperation for bleeding	5 (1.1%)
Unplanned major amputation	3 (0.7%)
Compartment syndrome	1 (0.2%)

* Creatinine increase more than 1 mg/100 mL.

postoperative complications. Early graft closure occurred in 27 (6%) instances within 30 postoperative days, with seven in the first day and 19 within the first 10 days. Eighteen of these early failures were in infrapopliteal grafts. The likely causes of early occlusion are tabulated in Table 4, with hypercoagulability and poor distal run-off most common. Technical problems referable to the *in situ* method such as retained valve leaflets, valvulotome injury, or kinks occurred in five of 27 early occlusions. Operative death within the first 30 days after surgery occurred in nine patients (2%) because of myocardial infarction (7), pneumonia (1), and multisystem organ failure (1).

Mean postoperative follow-up was 20.4 months (range, 1 to 81.5 months), and 352 grafts (80%) were followed to known end points. Graft surveillance identified 18 stenotic grafts (4%) that were revised initially while still patent by percutaneous balloon angioplasty (7), patch angioplasty (8), or distal bypass modification (3). Over the course of follow-up, these 18 grafts required a total of 30 revisionary procedures to maintain patency. Among 68 grafts (15%) that occluded during follow-up, 36 (8%) underwent initial disobliteration by thrombolysis (15) or thrombectomy (16). Seventeen grafts required no revision after disobliteration, and causative lesions were treated in 19 grafts by balloon angioplasty (4), patch angioplasty (12), or distal bypass modification (3). These 36 grafts required a total of 52 revisionary procedures in the effort to maintain patency during follow-up. Among the 32 occluded grafts not revised, 13 were replaced by a new graft, 12 underwent no further surgery, and 7 resulted in amputation.

Life-table analysis indicated overall 5-year rates of primary patency of 72%, primary revised patency of 78%, and secondary patency of 83% (Table 5, Fig. 1). Overall femoropopliteal graft success was notably improved from a primary patency of 78% to primary revised patency of 84% by revision of stenoses in patent grafts and to secondary patency of 86% after revision of occluded grafts ($p < 0.05$, Table 6). Above-knee femoropopliteal grafts fared no better than below-knee femoropopliteal grafts ($p > 0.1$). Although 5-year primary patency (63%) and primary revised patency (71%) were less ($p < 0.03$) for infrapopliteal grafts than for popliteal grafts (78% and 84%, respectively), there was no significant difference in secondary patency of infrapopliteal (78%) compared with popliteal (86%) grafts ($p = 0.074$) (Table 7, Fig. 2). Infrapopliteal graft patency was not diminished in the presence of diabetes, and grafts employing the peroneal artery as an outflow vessel performed as well as grafts to the other tibial vessels. The 18 inframalleolar grafts performed remarkably well over short-term follow-up. Overall 5-year primary and primary revised patency for patients bypassed for claudication (81% and 85%, respectively) were significantly better than for critical ischemia (66% and 75%, respectively) ($p < 0.05$), but secondary patency was similar for claudication (86%) and critical ischemia (81%) ($p = 0.14$) (Table 8, Fig. 3).

The overall 5-year limb salvage rate was 88%. Among the 141 patients who presented initially with claudication, only four (3%) limbs were amputated during the follow-up period, compared with a limb salvage rate of 84% in the 299 patients presenting with critical ischemia, in whom 30 amputations (10%) were performed ($p < 0.001$). The overall 5-year cumulative patient survival rate was 66%. The survival rate among claudicators was 73% at 5 years, compared with a survival rate of 60% among patients presenting with critical ischemia ($p = 0.08$).

Discussion

Evolution of small-vessel operative technique during the last decade has had a dramatic impact on the applicability of all forms of autogenous infrainguinal revascularization[8,17] including strategies emphasizing the *in situ* saphenous vein. Since its description by Hall[2] and popularization by Leather et al.,[4,5,16,18] simplification of the *in situ* method has made it a standard part of the surgical repertoire. The *in situ* saphenous vein has unique appeal for revascularization of patients with advanced critical ischemia due to infrapopliteal occlusive disease. Bypass to the calf and ankle level by simple transposition of the distal end of the vein to a small adjacent artery is

TABLE 4. *Causes of Graft Occlusion Within 30 Days of* In Situ *Saphenous Vein Bypass*

Cause	Number
Hypercoagulability	9/27 (33%)
Inadequate distal run off	7/27 (26%)
Technical error	6/27 (22%)
Systemic hypotension	5/27 (19%)

TABLE 5. *Five-year Cumulative Patency of 440* In Situ *Saphenous Vein Grafts**

	Interval (mos.)	No. of Grafts at Risk	No. of Grafts Failed	No. of Grafts Withdrawn Patent	Interval Patency (%)	Cumulative Patency (%)	Standard Error (%)
Primary Patency							
	0–3	440	42	80	89.5	89.5	1.5
	3–6	318	16	29	94.7	84.8	1.8
	6–12	273	10	47	96.0	81.4	2.1
	12–24	216	6	63	96.8	78.8	2.3
	24–36	147	4	52	96.7	76.2	2.5
	36–48	91	4	45	94.2	71.7	3.2
	48–60	42	0	30	100	71.7	3.2
Primary Revised Patency							
	0–3	440	36	79	91.0	91.0	1.4
	3–6	325	15	31	95.2	86.6	1.8
	6–12	279	8	48	96.9	83.9	1.9
	12–24	223	5	66	97.4	81.8	2.1
	24–36	152	2	55	98.4	80.4	2.3
	36–48	95	2	48	97.2	78.2	2.7
	48–60	45	0	32	100	78.2	2.7
Secondary Patency							
	0–3	440	40	82	92.7	92.7	1.2
	3–6	329	11	31	96.5	89.4	1.5
	6–12	287	8	50	97.0	86.8	1.8
	12–24	229	4	69	98.0	85.0	1.9
	24–36	156	2	56	98.4	83.7	2.1
	36–48	98	1	50	98.6	82.5	2.4
	48–60	47	0	33	100	82.5	2.4

* See text for definitions of primary, primary revised, and secondary patency.

logical, direct, and minimally traumatic. Even with the origin of such long grafts at the common femoral artery, our experience demonstrates that long-term patency and limb salvage rates are highly satisfactory.

Among a number of solutions to the problems of venous valve lysis and arteriovenous fistula control intrinsic to the *in situ* method, the techniques described have worked well in our hands. Exposure of the saphenous vein through a continuous incision allows complete valve lysis by the modified Mills valvulotome, with minimal apparent vein injury. In addition, the open method greatly facilitates ligation of venous side branches. Significant residual arteriovenous fistulas are easily detected by intraoperative Doppler ultrasound and completion arteriography. Although all fistulas may not need ligation[5,19] and most of the lateral branches connect only to the subcutaneous capillary bed, some of these branches develop stasis thrombosis, resulting in painful postoperative superficial phlebitis. We consequently recommended ligation of all visible venous tributaries. Because the open method contributed to an 8% incidence of wound complications in our series, recent efforts have been directed

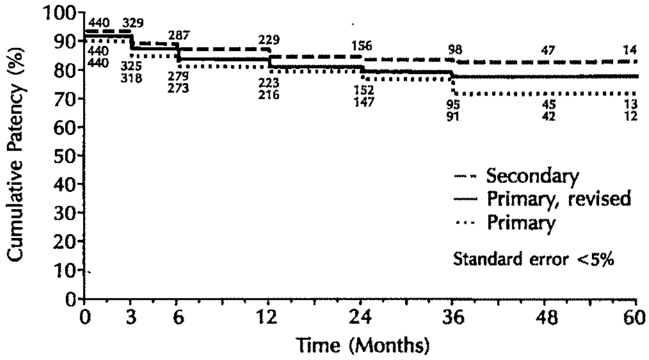

FIG. 1. Cumulative primary, primary revised, and secondary patency of 440 *in situ* saphenous vein grafts (see text).

TABLE 6. *Five-year Cumulative Patency for* In Situ *Saphenous Vein Bypass 1983 to 1990**

Subgroup	n	Primary (%)	Primary Revised (%)	Secondary (%)
All grafts	440	72	78	83
Femoropopliteal	240	78†	84†	86
Above knee	79	72	86	88
Below knee	161	82	83	85
Infrapopliteal	200	63†	71†	78
Claudication	141	81†	85†	87
Critical ischemia	299	66†	75†	81
Diabetes	168	76	80	81
No diabetes	272	70	80	80

* Standard error < 7%; †$p < 0.05$.

TABLE 7. *Five-year Cumulative Secondary Patency of 440* In Situ *Saphenous Vein Grafts, by Distal Anastomosis*

Interval (mos.)	No. of Grafts at Risk	No. of Grafts Failed	No. of Grafts Withdrawn Patent	Interval Patency (%)	Cumulative Patency (%)	Standard Error (%)
Popliteal						
0–3	240	15	40	94.6	94.6	1.5
3–6	188	3	19	98.3	93.0	1.8
6–12	166	4	25	97.4	90.6	2.1
12–24	137	3	44	97.4	88.2	2.4
24–36	90	2	27	97.4	85.9	2.9
36–48	61	0	29	100	85.9	2.9
48–60	32	0	23	100	85.9	2.9
Infrapopliteal						
0–3	200	25	42	90.5	90.5	2.2
3–6	141	8	12	94.1	85.2	2.7
6–12	121	4	25	96.3	82.0	3.1
12–24	92	1	25	98.8	81.0	3.2
24–36	66	0	29	100	81.0	3.2
36–48	37	1	21	96.3	78.0	4.3
48–60	15	0	10	100	78.0	4.3

$p = 0.07$ at 5 years.

at developing less invasive techniques for valve lysis and branch ligation without compromising the documented precision, predictability, and safety of the Mills valvulotome. We are evaluating the efficacy of angioscopy[20,21] in reducing the length of the skin incision, wound complications, and length of hospital stay. The length of postoperative recovery is most directly related to the indication for surgery, and many patients with disabling claudication or uncomplicated rest pain can be discharged from the hospital within 5 days of surgery.

Large series of *in situ* saphenous vein grafts have been published recently by Leather et al.[5] and Bandyk et al.[6] with results quite comparable to our own (Table 9). Modern series using reversed greater saphenous vein have also demonstrated excellent results,[8,22] testimony to the general impact of advances in technique. Using these techniques, Harris et al.[23] have found by randomized prospective trial that *in situ* and reversed greater saphenous vein bypass are equally effective at 3 years in the femoropopliteal position. Our own experience with both methods for bypass to the infrapopliteal level, however, indicates a clear superiority of grafts using *in situ* vein.[7] Conversely Taylor et al.[8] have achieved overall results in 285 reversed greater saphenous vein grafts very similar to our *in situ* experience in a very comparable patient group.

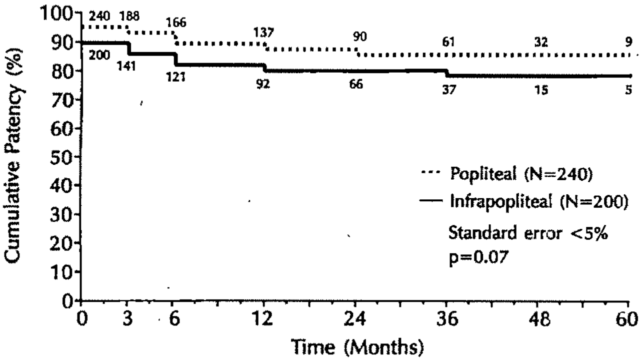

FIG. 2. Comparison of cumulative secondary patency of *in situ* saphenous vein grafts to popliteal and infrapopliteal arteries (Mantel-Cox log rank comparison at 5 years).

In all grafts, but particularly in those to the infrapopliteal level, patency is compromised by early perioperative failure, mid-term graft or anastomotic myointimal hyperplasia and late progression of disease in the inflow or outflow arteries.[14,15] Our experience of 6% graft thrombosis within 30 days of surgery is typical of other recent series,[5,24] with 18 of 27 such failures in infrapopliteal grafts. Analysis disclosed systemic hypotension, technical error, inadequate distal run-off, and hypercoagulability as the most probable causes of early graft occlusion. It would appear that improved patient selection, operative technique, and perioperative care can further reduce this complication. In addition, because of the apparent importance of hypercoagulability, before operation we screen patients undergoing infrainguinal reconstruction for presence of heparin-associated platelet activation and lupus anticoagulant.[25]

There is growing recognition[13,22,26–28] of the importance of postoperative graft surveillance to detect early and mid-term myointimal hyperplasia within the vein graft or at the anastomotic regions. The subcutaneous location of *in situ* saphenous vein grafts greatly facilitates monitoring with duplex ultrasound to sample overall graft velocity and to interrogate areas of stenosis. It is clear that revision of stenosis before occlusion yields long-term patency sim-

TABLE 8. *Five-year Cumulative Secondary Patency of 440* In Situ *Saphenous Vein Grafts, by Indication for Surgery*

Interval (mos.)	No. of Grafts at Risk	No. of Grafts Failed	No. of Grafts Withdrawn Patent	Interval Patency (%)	Cumulative Patency (%)	Standard Error (%)
Claudication						
0–3	141	6	16	95.5	95.5	1.8
3–6	119	0	12	100	95.5	1.8
6–12	107	1	17	99.0	94.5	2.0
12–24	89	1	26	98.7	93.3	2.0
24–36	62	2	22	96.1	89.7	3.4
36–48	38	1	17	96.6	86.6	4.4
48–60	20	0	14	100	86.6	4.4
Critical ischemia						
0–3	299	31	65	88.4	88.4	2.0
3–6	203	3	20	98.4	87.0	2.1
6–12	180	7	33	95.7	83.2	2.4
12–24	140	2	44	98.3	81.8	2.6
24–36	94	1	34	98.7	80.8	2.8
36–48	59	0	32	100	80.8	2.8
48–60	27	0	19	100	80.8	2.8

$p = 0.14$ at 5 years.

ilar to that experienced by unrevised grafts.[6] Theoretically by using the appropriate surveillance strategy and threshold for intervention, residual and progressive stenoses can be detected and corrected early enough to completely obviate occlusion resulting from lesions within the vein graft itself.

Recurrence of symptoms and decreases in segmental limb pressure are relatively insensitive indicators of impending graft failure compared with duplex ultrasound.[13,28] Using a reduction in overall graft velocity to less than 0.45 m/second as a threshold for intervention, Bandyk et al.[6] have succeeded in enhancing 4-year *in situ* vein primary patency of 62% to secondary patency of 85% in exchange for a reoperation rate of 28% (Table 9). In 10% of revisions, the vein was found occluded. Using a surveillance strategy that has relied largely on segmental limb pressures and only more recently on duplex ultrasound, we have been able to improve a 72% overall primary patency to 83% secondary patency, with a revision rate of 12%. In 66% of these revisions, the vein had occluded. Assuming that many of our occlusions might have been prevented by a more aggressive reoperation rate, our secondary patency would be even more encouraging. It is clear that further work using duplex ultrasound and other noninvasive monitoring methods will be needed to clarify the optimal surveillance protocol.

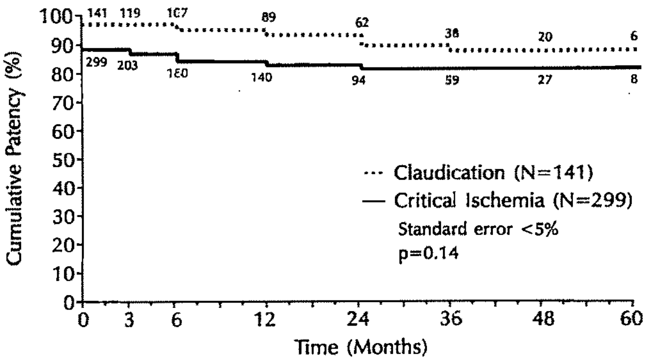

FIG. 3. Comparison of cumulative secondary patency of *in situ* saphenous vein grafts for claudication and critical ischemia (Mantel-Cox log rank comparison at 5 years).

After even a short period of thrombosis, graft longevity is severely reduced. Contact of the vein with thrombus and subsequent disobliterative efforts appear to accelerate the process of reactive hyperplasia in the vein wall. In our experience use of fibrinolytic therapy has had no advantage over surgical thrombectomy as a means of clearing thrombus, as both methods combined with correction of the underlying lesion result in disappointing prolongation of patency.[29] Nonetheless, efforts to restore patency to occluded *in situ* grafts are worthwhile, as our secondary patency rates were somewhat higher than the primary revised rates. We would recommend careful selection of appropriate candidates for revision, however, as complete replacement of an occluded vein may ultimately be the best strategy in many instances.

At risk of further confusion, our patency data has been presented using three different curves in an effort to clarify the impact of graft revision for nonocclusive lesions (primary revised patency), as distinct from the impact of revisions after occlusion (secondary patency). Most of the

TABLE 9. *Comparison of Experience with Greater Saphenous Vein Bypass*

Author	Method	n	Critical Ischemia (%)	Infrapopliteal Graft (%)	Primary Patency (%)*	Grafts Revised (%)	Secondary Patency (%)†
Leather 1988	ISV	1,038	91	64	59	11.5	76
Bandyk 1989	ISV	250	93	67	62	28	85
Present series	ISV	440	68	46	72	12	83
Berkowitz 1987	RV	102	86	100	47	19	70
Fogle 1987	RV	535	77	16	N/A	6	63
Taylor 1990	RV	285	73	37	80	N/A	84

ISV, *in situ* vein; RV, reversed vein.

* Primary patency, patency without any revision.

† Secondary patency, patency after revision for stenosis or occlusion except Berkowitz (revisions for stenosis only).

All patency rates are cumulative at 5 years except Bandyk (4 years).

literature includes only grafts with no revision in primary patency tables, and all grafts (unrevised, and revised patent or occluded one or more times) on secondary patency tables. The Ad Hoc Committee on Reporting Standards of the National Vascular Societies has suggested that primary patency include unrevised and revised patent grafts, using secondary patency tables only after graft occlusion.[30] Our scheme reflects both common practice and Ad Hoc Committee recommendations.

Using the *in situ* greater saphenous vein as a cornerstone, we have made an effort to pursue a policy of all autogenous infrainguinal reconstruction since 1985.[31] Primary amputations have been necessary in only 1.3% of patients presenting with atherosclerotic occlusive disease below the inguinal ligament, and autogenous revascularization methods have been applicable in 90%. The *in situ* greater saphenous vein has been available in 66% of reconstructions, despite 25% of patients who presented after previous ipsilateral surgery. Limb salvage rates are nearly 90% at 5 years, and even in patients presenting with critical ischemia, 5-year limb salvage is possible in 85%. Improvement in long-term patient survival rates compared with years past reflects improvements in surgical and cardiac care despite more advanced systemic and peripheral atherosclerosis. Although infrainguinal revascularization clearly remains palliative, it is increasingly important to provide maintenance-free durable relief from ischemia, given the increased longevity of the patient population.

The current series represents the entire experience with *in situ* greater saphenous vein bypass on the vascular service at Brigham and Women's Hospital and supports continued use of this method as the preferred approach to infrainguinal arterial occlusive disease. In particular, reconstructions below the popliteal artery in patients with advanced disease and diabetes are well served by this versatile and simple technique. Future efforts should be directed at further reducing wound morbidity and causes of early graft failure and at perfecting strategies for midterm graft surveillance with revision before occlusion. The underlying issue of myointimal hyperplasia after vascular intervention remains to be solved.

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DISCUSSION

DR. GEORGE JOHNSON, JR. (Chapel Hill, North Carolina): This series of bypass grafts below the inguinal ligaments continues to be the gold standard for surgeons who do vascular operations.

Based on experience with 652 patients followed by my colleague, Dr. Steven Burnham at the University of North Carolina Hospitals, we agree with their techniques and conclusions.

They have used reporting criteria developed by the vascular societies that use primary and secondary patency. Their data, therefore, emphasize the need for postoperative surveillance of the grafts in these patients.

Their data also reaffirm DeWeese and Robbs' study of 15 years ago that showed the life expectancy for these patients is roughly one third that of the rest of the population—a fact that needs to be considered when operating on these patients. It also raises the question of whether we should be more aggressive in performing or recommending coronary revascularization on these patients.

Our series differs slightly in that 90% compared to 70% were for ischemia; and 5%, compared to their 20%, were above-the-knee bypass grafts. For above-the-knee bypass grafts, we used translocated nonreversed saphenous veins with valve disruption.

Although we use *in situ* grafts for all infrapopliteal bypasses, perhaps the answer is to use vein, but to do it the way the surgeon doing the operation can do it best using reversed saphenous veins. Porter has the best primary patency of the series you reviewed. The randomized series from your institution may reflect your superior skill in doing *in situ* bypass grafts.

Your reports on hypercoagulability have interested us. We have been investigating the influence of the acute-phase reaction on this condition. In the immediate postoperative period, fibrinogen is increased and preliminary data suggest a decrease in protein C.

You state that you are now screening for heparin-associated platelet activation and lupus anticoagulant before operation. Why not antithrombin III, protein C, and protein S as well?

DR. CARLOS CHAVEZ (Brownsville, Texas): We continue to use the reverse saphenous vein graft because we have not found hard data and convincing data that the *in situ* grafts are superior to the reversed vein graft. However the presentation by Dr. Mannick may change our minds.

One way to avoid the use of below-the-knee distal anastomosis is the combination of open balloon angioplasty of any stenotic lesion in the popliteal segment and placement of the distal anastomosis above the knee.

We make our arteriotomy in the distal superficial femoral artery as if we were going to do a routine femoral popliteal bypass. And through this incision we introduce the balloon catheter to dilate any popliteal stenosed segment. We used this approach in the last 21 patients in whom a popliteal stenosis was present, and we have had very gratifying results.

How do you, Dr. Mannick, rate your results early and late with those using reverse saphenous vein grafts in both below or above the knee grafts?

DR. MAGRUDER DONALDSON (Closing discussion): This clearly is, as Dr. Johnson mentioned, a game of palliation. And despite discussion about the possible impacts of coronary bypass and improved coronary medical therapy, this group of patients does not survive nearly as long as the rest of the population. So what we are striving for is a simple, safe, and very effective means of revascularizing painful legs that has durability and does not require maintenance every 6 to 12 months. The *in situ* graft as practiced in this series and in others around the country comes closest to fitting this need.

We found that even in the above-knee circumstance where, indeed, only part of the graft remains completely *in situ*, it is simple to unroof the graft, connect the top end to the femoral artery and the lower end to the popliteal artery rather than take it out and reverse it. This ease and simplicity becomes more obvious the further down the leg you go.

There has been experience, in reference to Dr. Chavez' comments, with small vessel angioplasty. And although we also have used such angioplasty in some occasions before operation, there really is not sufficient evidence to support it as part of a durable, long-term solution when compared particularly with the excellent results that seem to be available through tibial grafts using the *in situ* method. The results are so satisfactory with distal revascularization that, in fact, we have been moving farther and farther down the leg using this method.

The hypercoagulability, we think, is an important problem in the first 30 days. About one third of our patients, either by proofs or strong influence, appear to have occluded in the presence of abnormal hypercoagulability. We have been looking prospectively in an attempt to identify people with heparin-associated platelet activation and lupus anticoagulant because they seem to be the most nasty critters. At one point we also surveyed for protein C, protein S, antithrombin III, plasminogen abnormality, and fibrinogen and found the yield so small that the added cost of including them prospectively on a routine basis would not really be justifiable. So at this point we are continuing to look for heparin antibody and lupus anticoagulant. If we run into a clotted graft, we work backward trying to understand whether that patient in particular had one of these less common problems.

The issue of surveillance for long-term management needs some more work to try to identify patients before they get into trouble and to avoid having to resurrect a graft after it has occluded.

Poisonous Snakebite in Central Texas

Possible Indicators for Antivenin Treatment

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Sixty-seven patients hospitalized for poisonous snakebite between 1975 and 1990 were managed by elevation, tetanus prophylaxis, intravenous fluids and antibiotics, and often by a limited excision of the bite site in the Emergency Department, with sequential laboratory studies as needed. Antivenin was used for systemic envenomation, and 23 of the 67 patients (34%) received 133 vials. Thirteen of the twenty-three patients (56%) had adverse reactions to the antivenin. Two significant observations arose. First age was an indicator. Eleven of eighteen patients 12 years or younger (61%) received antivenin, whereas 12 of 49 patients older than 12 years (24%) received antivenin ($p = 0.0085$, Fisher's exact test). Second species of snake was an indicator. Sixty-two snakes were identified (93%). Of 39 rattlesnake (*Crotalus* and *Sistrurus*) bites, 20 patients received antivenin (53%), but of 23 copperhead and water moccasin (*Agkistrodon*) bites, only three patients(12.5%) received antivenin ($p = 0.0025$). Antivenin may be indicated for use in systemic rattlesnake envenomation, especially in younger patients.

THE CLINICAL MANAGEMENT of poisonous snakebite continues to stir controversy. Advocates of antivenin (*Crotalidae*) polyvalent therapy (Wyeth-Ayerst Laboratories, Philadelphia, PA) record its benefits and suggest the potentially harmful result of aggressive surgical treatment.[1,2] Others eschew antivenin to recommend excisional therapy,[3] and some favor excision/fasciotomy therapy,[4,5] sometimes using antivenin. Recently a major series report suggests that neither antivenin nor surgical excision is needed in the majority of snakebite cases.[6]

Stimulated by the controversy, we established a 15-year institutional review to assess our experience in treating poisonous snakebites, looking especially for possible indicators to administer antivenin.

Methods

From 1975 through January 1990, 67 patients were admitted for treatment of poisonous snakebite at Scott and White Hospital, Texas A&M University College of Medicine in Temple, Texas. Patient ages ranged from 1 to 76 years. Nine patients were aged 6 years or younger, and 18 were 12 years or younger. The average age was 32.5 years. Forty-eight patients were male, and 19 patients were female. The average time from injury to hospital presentation was 1.9 hours, with a range of 10 minutes to 12 hours.

The biting snake was identified in 93% of the cases. Either the victim or an observer at the scene made positive identification or the snake was identified using a color atlas at the Emergency Department. All snakes identified were native to Central Texas, where 11 species of poisonous snakes are indigenous, including the western diamondback (*Crotalus atrox*), the canebrake rattlesnake (*Crotalus horridus atricaudatus*), the timber rattlesnake (*Crotalus horridus horridus*), northern blacktailed rattlesnake (*Crotalus molosus molosus*), and the prairie rattlesnake (*Crotalus viridus viridus*). A second genus of Central Texas rattlesnake includes the western massasauga (*Sistrurus catenatus tergeminius*), the western pigmy (*Sistrurus miliarius streckeri*), and the desert massasauga (*Sistrurus catenatus edwardsi*).[7]

A third genus of poisonous snakes native to Central Texas includes the broad-banded copperhead (*Agkistro-*

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don contortrix laticintus), the southern copperhead (*Agkistrodon contortrix contortrix*), and the western cottonmouth moccasin (*Agkistrodon piscivorus leucostoma*).[7]

According to type of snake, 39 victims were bitten by rattlesnake (58%), 20 by copperhead (30%), 3 by cottonmouth moccasin (4%), and 5 by an unidentified snake (7%). Medical record review also included location of bite wound, circumstances of the biting event, patients' clinical signs and symptoms, steps in early management, laboratory reports, severity of injury with attempts at retrospective grading of envenomation, use of antivenin, requirements for further surgery, and eventual outcome.

Results

Initial care began with verification of bite wound by poisonous snake. Some patients brought to the Emergency Department a dead snake in a bag, and one even brought a live one. The history of snakebite was then confirmed by documentation of one or more fang marks at the bite site. The distance between fang marks was used as a guide to size of snake and gave rough indication of severity of envenomation to be expected. Physical findings and complaints of pain confirmed envenomation, but severity of these signs varied widely at the time of initial presentation to the emergency department, depending partially on elapsed time since the biting. The sooner the patient came to the emergency department, the more unimpressive were the presenting physical findings. Several patients thought initially to have sustained no envenomation, but who had a positive history and fang marks, subsequently, in the ensuing hours developed pain, marked swelling, and ecchymosis. All patients with fang marks were admitted for close observation because initial grading was unreliable as a guide to the severity of envenomation. Clinical signs and symptoms evolved progressively in 6 to 12 hours after biting, revealing the degree of envenomation. Subsequent retrospective grading also proved imprecise.

No patients were bitten on the job, but all were bitten during what generally could be termed recreation—such as hunting, fishing, gardening, outside play, and snake round-ups. Most bites occurred during spring and summer, and the right hand (27) and left foot (21) were the most common bite sites.

Initial laboratory studies included complete blood count with platelet count and clotting studies (prothrombin time, partial thromboplastin time, fibrinogen levels, and fibrin split products.) These studies were repeated at 6-hour intervals until stable. Initial treatment often included a limited, early excision of the bite wound, especially for rattlesnake bites. Removal of a small 'plug' of skin and subcutaneous tissue, to include the fang marks, was chosen when anatomically convenient. Sometimes an incision was made connecting two fang marks. This procedure usually was carried out in the emergency department. Fascial integrity can be assessed through this wound.

The small wounds resulting from bite excision sometimes produced voluminous outpouring of serous drainage in the first several days, thus partially decompressing the extremity.

Wound sites were maximally elevated to protect distal tissue from vascular compromise associated with swelling. Upper-extremity bites were elevated by nonconstricting stockinette sling, and lower extremity bites were elevated with multiple pillows and bed positioning. Swelling was centripetal, and regional lymph nodes routinely became tender. Swelling and ecchymosis often progressed to the trunk.

Patients were administered intravenous fluids and antibiotics, tetanus toxoid, and analgesics as needed. In the early years of the review, four patients were administered systemic steroids. On review no specific benefit could be attributed to steroid therapy. Patient condition was monitored continuously. If severe systemic symptoms developed, such as marked nausea and vomiting, central nervous system signs, cardiovascular shock, or deterioration of clotting parameters, the patient was skin tested for sensitivity to antivenin (*Crotalidae*) polyvalent. If nonreactive to skin test, patients with severe systemic signs and symptoms were moved to a monitored bed in the surgical intensive care unit and administered intravenous antivenin. If no allergic symptoms developed, multiple vials were administered according to package insert guidelines (Table 1). Twenty-three patients received 133 vials. Mild itching

TABLE 1. *Guidelines for Antivenin Administration*

Severity	Manifestations	Amount of Antivenin
No envenomation	No local or systemic signs	0
Minimal envenomation	Local swelling, no systemic signs, normal lab	2–4 vials
Moderate envenomation	Extended swelling, 1 or more systemic manifestation, lab abnormalities	5–9 vials
Severe envenomation	Marked local response, severe systemic manifestations	10–15+ vials

From Wyeth, Antivenin (Crotalidae) Polyvalent (equine origin) package insert, 1984.

or hives were treated with intravenous Benadryl® (Parke-Davis, Morris Plains, NJ). When severe allergic reactions such as anaphylactic shock developed, however, the antivenin was immediately stopped and the patient was resuscitated.

Clotting abnormalities seemed to be of two varieties. One was a consumption-type coagulopathy with very low platelet count and disseminated intravascular coagulation. The other was a heparinlike syndrome with prolongation of prothrombin time and partial thromboplastin time but with normal platelet count. Mixed-coagulopathy patterns also were noted. Both types of coagulation abnormalities occasionally returned toward normal within minutes of intravenous antivenin administration, but not in all patients. Some antivenin recipients demonstrated slow recovery of clotting aberrations in a way similar to untreated patients. Relief of gastrointestinal symptoms frequently followed antivenin administration, but again, at a variable rate.

Of the 67 patients hospitalized, 23 were treated with antivenin for severe systemic symptoms of envenomation (Table 2). Twenty of these twenty-three severely injured patients (87%) were rattlesnake (*Crotalus* and *Sistrurus*) bite victims, constituting 53% of the 39 total rattlesnake bites. The remaining three patients treated with antivenin for severe systemic symptoms were bitten by copperhead (two) and cottonmouth moccasin (one) of genus *Agkistrodon.* They constituted 13% of the 23 *Agkistrodon* bites. Comparing species of biting snake as an indicator for antivenin use, 53% of *Crotalus* and *Sistrurus* bites were treated, but only 13% of *Agkistrodon* bites were treated ($p = 0.003$ Fisher's exact test). All three of these *Agkistrodon* bites were treated before 1980. Our current practice is to withhold antivenin for *Agkistrodon* bites because the symptoms are less severe and resolve sooner than do rattlesnake bite symptoms.

Analysis of patient ages (Table 2) showed that 18 bite victims were 12 years of age or younger and that 11 of these (61%) received antivenin for signs of systemic envenomation. By contrast, 12 (24%) of 49 older patients received antivenin ($p = 0.0085$). Of the 12 patients developing severe coagulopathy, 9 were children, whereas only 3 were adults ($p = 0.0002$).

TABLE 2. *Antivenin Treatment Demographics*

Patient Groups	Number of Patients	Patients Who Received Antivenin	%
Rattlesnake bites	39	20	53
Copperhead bites	20	2	10
Water moccasin bites	3	1	33
Unidentified	5	0	0
12 years old or younger	18	11	61
Older than 12 years old	49	12	24
Total patients	67	23	34

TABLE 3. *Further Surgery Demographics*

Patient Groups	Number of Patients	Patients Receiving Further Surgery	% of Patients Receiving Further Surgery
Rattlesnake bites	39	16 (41%)	84
Cooperhead bites	20	1 (5%)	5
Water moccasin bites	3	2 (67%)	11
Unidentified	5	0	0
12 years old or younger	18	9 (50%)	47
Older than 12 years old	49	10 (20%)	53
Total patients	67	19 (28%)	100

Adverse reactions to antivenin were recorded in 13 of 23 hospitalized patients treated with antivenin (56%). Nine of these patients had severe anaphylactic reactions with shock symptoms. This experience leads us to give antivenin in the intensive care setting. The mean age of hospitalized patients showing no adverse allergic reactions to antivenin was 18.2 years, whereas those with adverse allergic reactions had a mean age of 34.5 years. Although younger patients were sicker and more often received antivenin, they tolerated antivenin therapy better, having fewer adverse reactions. The frequency of serious allergic reactions, however, is a major restraint on our decision to chose antivenin therapy.

During the hospital course, 19 patients required subsequent surgical procedures (Table 3). Of these, 16 were rattlesnake bite victims (84%), 2 were moccasin bites, and 1 was a copperhead bite. Rattlesnake bites (16/39) were much more likely than copperhead bites (1/20) to require further surgery ($p = 0.005$). A 7-year-old patient, who was bitten by a copperhead on the left fifth toe, developed severe nausea and vomiting and a marked coagulopathy associated with dramatic swelling and impaired circulation in the left foot. Within the first 24 hours he had a pressure-releasing dorsal skin incision that was closed secondarily on day 6. No tissue was lost. This patient, treated in 1980, was also our last copperhead bite to receive antivenin. One of the two moccasin bite victims was similarly operated for severe lower-extremity swelling and distal ischemia with secondary closure and no tissue loss. The other moccasin bite requiring further surgery had a left long finger bite that led to finger-tip necrosis and distal interphalangeal amputation. The 16 rattlesnake patients requiring additional surgery included two arthrotomies for wash-out of joint penetration (one finger in an adult and one knee in a child). Fasciotomy was used whenever suspicion of subfascial envenomation led to concern for muscular compartment pressure syndrome.

One rattlesnake victim kept several 'pet' snakes in his house and regularly 'mainlined' small doses of venom intravenously in the mistaken effort to become tolerant. He was 'kissing' a large rattler when it bit him in the upper lip, causing marked facial swelling. Surgical release was performed by upper labial sulcus incision for submuscular elevation of the soft tissues of the central face at the periosteal level, resulting in outpouring of edema fluid. Eventual healing ensued with no tissue loss and no postoperative complications. A 55-year-old man, bitten on the left foot by a rattlesnake, was treated with ice before referral to Scott and White and sustained eventual skin necrosis on the foot and ankle. He had a surgically remediable arterial occlusive lesion that was repaired before soft-tissue reconstruction. The left foot wound was repaired, first by unsuccessful free flap transfer, and later successfully by cross-leg flap. Limb salvage was accomplished, but this patient was in the hospital for 57 days. One female competitor in the snake-bagging contest at a rattlesnake roundup was struck by a large rattlesnake that 'hung on' for a prolonged interval. Despite antivenin and surgical releasing incisions, marked tissue necrosis led to amputation of the index finger ray. Nine of the nineteen patients requiring subsequent surgery were aged 12 years or younger, a rate of 50% for the 18 children in the series (Table 3). Ten of forty-nine older patients (20%) required further surgery ($p = 0.03$). No patients died.

Average length of hospital stay (Table 4) for all patients was 5.6 days. Rattlesnake bite victims stayed an average of 7.8 days, whereas copperhead bite patients averaged 2.2 days. The three moccasin bite patients stayed 11, 5, and 1 days in the hospital. Using hospital stay as a severity index, rattlesnake bites kept patients in the hospital the longest. Further only two of the 20 copperhead bite patients stayed longer than 4 days in the hospital (6 days and 8 days), whereas nine of 39 rattlesnake bites stayed in the hospital over 10 days (10, 13, 14, 15, 17, 19, 19, 20, and 57 days). At the same time, 12 of 39 rattlesnake bite patients stayed 2 days or less in the hospital and clearly had minimal envenomation.

TABLE 4. *Length of Hospital Stay*

Patient Groups	Average Days in Hospital	Number of Patients in 10 or More Days	Number of Patients in 2 or Less Days
39 Rattlesnake bites	7.8	9 (24%)	12 (32%)
20 Copperhead bites	2.2	0	16 (80%)
3 Water moccasin	5.7	1 (33%)	1 (33%)
5 Unidentified	1.3	0	5 (100%)
67 Total patients	5.6		

Discussion

Although this series of 67 poisonous snakebites is not a large experience, it demonstrates several observations that may help us to understand some of the divergent recommendations in the snakebite literature.

First our study suggests that all United States pit vipers (*Crotalid* family), and pit viper bites, are not equal. Our rattlesnake (*Crotalus* and *Sistrurus*) bite patients more often manifested signs of severe envenomation, more often required additional surgery, more often received antivenin, and had a much longer average hospital stay than the copperhead (*Agkistrodon*) bite patients. Of course some rattlesnake bites produced minimal envenomation, but if a large rattlesnake inflicted significant envenomation, the patient would very likely be quite sick.

Snakebite series wherein rattlesnakes (*Crotalus* and *Sistrurus*) predominate, such as the comprehensive reports of Snyder et al.,[8] Glass,[4] and Grace and Omer,[5] document the severe injury caused by significant rattlesnake envenomation, including tissue necrosis, amputation, and death. Our rattlesnake experience supports these reports.

Other authors report snakebite series predominantly involving bites by copperhead and water moccasin (*Agkistrodon*),[6,9] or the mildly poisonous Northern Pacific rattlesnake (*Crotalus viridis oregansus*).[2] Burch et al.[6] report a larger series of 81 snakebites, but only 10 were rattlesnake bites. These 10 bites accounted for four of their five most severe envenomations. Their 45 copperhead bite patients had a relatively short hospital stay (2.5 days), comparing favorably with our average copperhead bite hospital stay of 2.2 days. Similarly a recent report by Wagner and Golladay[9] suggests management guidelines for (*Crotalid*) envenomation in a series of 29 young snakebite patients that included only three documented rattlesnake bites. Of the 26 remaining bites (*Agkistrodon* or unidentified), all but one was judged to be mildly or minimally envenomated. Only three bites were graded more severe—two rattlesnake and one moccasin. In our series the 20 copperhead bites were similarly less severely envenomated than the 39 rattlesnake bites.

Based on our experience and that reported by others, we believe that identifying the biting snake is an important aspect in establishing the therapeutic mind-set for the care of a snakebite patient. In doing so, some apparent contradictions in management recommendations are resolved. Burch et al.[6] and Wagner and Golladay[9] report series from our south-central United States region. Their series include few rattlesnake bites, and their recommendations for therapy are conservative, mostly advocating supportive care. Looking exclusively at our copperhead bite patients, we concur with these authors. We disagree, however, that management experience based largely on copperhead bites should be generalized to the management of all *Crotalid* (United States pit viper) bites.

Similarly when Snyder et al.,[8] Glass,[4] and Grace and Omer,[5] all dealing mainly with rattlesnake victims, advocate more aggressive medical and surgical treatment, we again concur. Our significantly envenomated rattlesnake bite patients suffered severe pain, marked coagulation defects, systemic symptoms, and tissue necrosis. We agree that aggressive medical and surgical therapy is appropriate for many rattlesnake bite victims, but we disagree that one can generalize from this experience to management recommendations for all *Crotalid* (US pit viper) bite patients. We also disagree with the influential report of Huang et al.[3] from a coastal Texas experience geographically similar to that of Burch et al.[6] Huang advocated an aggressive surgical excision approach to all poisonous snakebite patients without any genus identification of biting snake in the report. Our data cannot support the implicit assumption that all poisonous snakebites are the same and should therefore be treated similarly. In general rattlesnake bites are worse injuries than copperhead bites, and cottonmouth moccasin bites probably fall somewhere in between.

Secondly, our data show that younger patients suffered more severe envenomation syndromes than did adults. This observation is consistent with other reports.[5,8] On the other hand, Wagner and Golladay[9] suggest that poisonous snakebite in children can be managed conservatively, especially in copperhead bites. In addition, our data show that 9 of 12 severe coagulopathy reactions occurred in children, one of which was a copperhead bite. Whether this age group difference is related to weight, blood volume, surface area, or other factors is unknown.

Biochemical analyses of snakebite-related coagulation defects[10-13] suggest significant species differences among poisonous snakes. Not only are differences noted between Eastern diamondback rattlesnake (*Crotalus adamanteus*), which can cause a hypofibrinogenemia without profound thrombocytopenia,[13,14] and Western diamondback (*Crotalus atrox*), which can cause a consumptive-type coagulopathy with thrombocytopenia,[12,15] but also differences are noted among individual snakes in the same genus.[11,12] There is even variation of venom enzymatic content documented in the same rattlesnake at different times.[15] Moreover distinct differences between *Crotalus* and *Agkistrodon* venoms are noted both in their mechanism of enzymatic initiation of anticoagulation effect and in their potency to anticoagulate the victims.[13]

Indications for antivenin treatment remain uncertain and subject to debate. Analysis of our data shows that rattlesnake (*Crotalus* and *Sistrurus*) bites and juvenile patient age are two factors that correlate both with increased severity of envenomation and consequently with our selective decision to administer intravenous antivenin.

The answer to the question of when to give antivenin is not clarified by inspection of the antivenin (*Crotalidae*) polyvalent. It is developed by collecting concentrated serum globulins from horses immunized with the following venoms: *Crotalus adamanteus* (Eastern diamondback rattlesnake), *Crotalus atrox* (Western diamondback rattlesnake), *Crotalus durissus terrificus* (Tropical rattlesnake, Cascabel) and *Bothrops atrox* (Fer-de-lance).[16] The decision to treat with antivenin not only loads the patient with additional foreign animal proteins but also administers a product derived from equine exposure to snake venoms, two of four of which snakes do not even reside in the United States. Knowing the variations among native snake venoms, one must question the wisdom of giving patients antivenin against foreign snakes. The content of antivenin complicates a therapeutic decision already facing myriad variables.

Until the double-blind study called for by Lindsey[17] is published, the treating physician must weigh indications for antivenin therapy on an individual basis.

We recommend withholding antivenin therapy for copperhead snakebite patients in all but the most severe copperhead envenomations. Rattlesnake bites in our locale are capable of producing very severe envenomation syndromes, especially in young patients, and, therefore, we will continue to treat selected severely envenomated rattlesnake bite victims with antivenin. The species of snake and the age of patient may be possible indicators for its selected use.

Summarizing our treatment recommendations, we advocate early limited bite excision when anatomically convenient, following Snyder et al.,[8] who demonstrated removal of up to 75% of injected venom for up to 2 hours after the bite. We especially advocate excision of rattlesnake and cottonmouth moccasin bites. The injured part is then elevated to minimize swelling, seeking to avoid releasing incision/fasciotomy. Coagulation studies and clinical condition are monitored. Surgical releasing incisions are used for any signs of circulatory compromise in peripheral tissues or to release envenomated muscular compartments. No attempt is made to excise ecchymotic tissue at the time of these later operations. Secondary closure is sought as soon as decreased swelling allows. Intravenous antivenin (*Crotalidae*) polyvalent is given to patients who manifest systemic signs of severe envenomation, mostly for rattlesnake bites, especially in children.

Further surgery is chosen as needed in the repair of necrotic tissues. This occurs predominantly in rattlesnake bites.

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DISCUSSIONS

DR. CHARLES H. WATT, JR. (Thomasville, Georgia): I became interested in the treatment of snakebites 37 years ago when Dr. L. M. Klauber of San Diego in his classic two-volume series of rattlesnakes stated that the Eastern diamondback rattlesnake was probably the most dangerous in America.

We have 272 poisonous snakebites treated since 1953; 94, as you see, were caused by the Eastern diamondback. Most of our bites were from this species and the Florida cottonmouth. There were no deaths. There were no deformities, except in one case in which cryotherapy was used at another institution.

Two reasons, perhaps, account for the difference in our treatment. Dr. White is faced with a 2-hour presentation time, as you noted a minute ago, compared to our 40 minutes. The difference in species, as he noted, must be taken also into account, which may be why we are using antivenin much more frequently and in larger amounts in treating our Eastern diamondback and canebrake rattlesnakes.

We are acutely aware of the disadvantages of horse serum in antivenin also, but without antivenin, we would have several deaths—which happened in our hospital before 1953, but not in our series.

Even with a negative horse serum test, we administer epinephrine and antihistamine, which reduces considerably the incidence of anaphylaxis, and the frequent occurrence of serum sickness is controlled with steroids and an antihistamine.

In severe cases we may give antivenin as a 5-minute push, but we rarely continue the push after the first few vials, then switch to a more dilute solution. Due to the above routine, we almost never see coagulopathy. We average 18.7 vials of antivenin per patient who has been bitten by the Eastern diamondback and canebrake rattlesnakes. We give an average of 9.2 vials of antivenin to the victims of the adult cottonmouth.

I don't know whether that shows up very well, but this is a good example of a child bitten on the left leg three times by an Eastern diamondback snake with no excision and who received 22 vials of antivenin. She had no deformity.

We have had to do only one fasciotomy in this series of 272 cases. This followed cryotherapy in another hospital, even though adequate antivenin had been given. Bill Lorimer of Ft. Worth, Texas, and a member of this organization, feels as I do, that if adequate antivenin is given one rarely needs surgery.

Because 21% of all snakebites occur in the digits, we have done 80 digit dermotomies and think it is helpful and have described this procedure in the literature.

Dr. White, I'd like to ask you how many of your cases with antivenin had severe anaphylaxis. I agree a double-blind study would certainly be in order, as you mentioned.

DR. RICHARD BAKER (Lubbock, Texas): At Texas Tech we see 10 to 15 bites a year, exclusively the Western diamondback or the prairie rattler.

Our current management is immediate exploration and decompression because in the past approximately one quarter of our patients required subsequent decompression after antivenin treatment, which was considered a failure.

This slide shows an 11-year-old who had received eight vials of antivenin in another institution, came in with a cold, insensate leg and required extensive debridement, which we closed a week later. And the child, again, has no significant disability.

I do not know an end point for the use of antivenin. One of our emergency room physicians regionally uses 100 to 125 vials of antivenin for significant envenomation. That's $10,000 to $12,000, which I find intriguing, to say the least.

I would ask Dr. White, if you do decide to use the antivenin, what's your end point?

DR. TIM PENNELL (Winston-Salem, North Carolina): Drs. White and Weber have undertaken another good approach in attempting to answer the very fundamental yet frustrating question of when to use antivenin. It remains a controversial issue, as we have learned in this discussion, and indeed indicators are needed. The authors make three very good points in their manuscript. (1) Antivenin is not a benign mode of treatment. (2) All poisonous snakes and snake bites, even occurring in the same genus, are not equal. Incidentally those of us who are confronted with managing such injuries should be mindful that 20% of all pit viper bites do not result in any envenomation. (3) The use of antivenin should be based on the degree of systemic envenomation and as presented, predictors of this are age and size of the patient and snake type and size. Of course the unknown factor is the dose or amount of venom that is injected and this can be measured accurately only on the basis of clinical response. Furthermore one must take into consideration the basic health status of the victim in connection with these other factors.

If we combine and compare this series with ours reported in 1986 and now containing 119 patients, the distribution of type of snake and results remain the same. Our series is dominated by copperhead bites, whereas the Scott-White clinic experience is predominated by rattlesnakes. They are faced with the famous rattlesnake round-up in their area. Even with this variation, we both are stressing that copperhead and cottonmouth bites, even with envenomation, rarely if ever require the use of antivenin.

One final point, which is often overlooked, and then a question. The person who sustains a poisonous snake bite either because of where they live, their vocation, or hobbies and outdoor activities, usually returns to the same or similar locations. They are, therefore, at increased risk for subsequent snake bites. We should not sensitize these people with the inappropriate use of horse serum-based antivenin. I would be most interested if any of the patients in this series sustained more than one snake bite or strike on different occasions.

DR. JON BURCH (Houston, Texas): As mentioned by the authors of this paper, we do not use and have not used antivenin at the Ben Taub Hospital, although admittedly most of our patients have suffered from bites of the copperhead. However we have had some serious bites, and we have preferred to treat those with the more commonly used methods of the modern intensive care unit, including careful observation and timely intervention based on the patient's condition.

I would like to ask two questions of the authors. Were any blood products used to treat coagulopathies that occurred in patients who were treated with antivenin? Was there any evidence that patients treated with antivenin had less tissue necrosis than those who were not?

DR. WAYNE SCHWESINGER (San Antonio, Texas): Obviously some of these questions are becoming repetitive. I want to remind those of you left in the audience, however, that when controversies persist in surgery, one approach to answering those controversies is to go back to the laboratory.

That brings to mind the fact that a resident recently conducted a study in our laboratory on this very issue. Dr. Ron Stewart developed, validated, and then studied a hind-limb rabbit model of a fixed-dose diamondback rattler envenomation and noted that, in fact, the use of antivenin was associated with decreased swelling, improved survival, and retention of muscular activity when compared to either no specific treatment or the use of wide debridement.

So it appears that antivenin then would be justified in patients not only with severe systemic illness but would also be justified in those patients who had severe envenomation but no severe systemic illness. That is, a patient such as the one who has extremity injury or envenomation with massive swelling but no systemic signs. Furthermore it is suggested by this data that preservation of muscle function can be achieved by the administration of antivenin alone.

So the question would be then, first, do the authors feel that the administration of antivenin may result in preservation of muscle function and, therefore, would be justified in that special circumstance?

I am also interested in the fact that the rate of anaphylaxis was so high. In point of fact, an anaphylaxis rate in excess of 40% is much higher than that reported by other authors who cite rates of 1% to 10%. Is there a reason for this? Is the rate changing in the more recent time interval?

I applaud the authors' use of conservative therapy and antivenin and the avoidance of massive debridements.

DR. ROBERT A. WEBER (Closing discussion): Talking about antivenin use is often like trying to answer the question whether Miller Lite beer tastes great or is less filling. With the comments we have received this afternoon, I find that this indeed holds true.

We view the treatment of snakebites as involving in two areas, local injuries and systemic involvement. We think a local treatment, surgical excision of the bite wound, is best suited for the management of local tissue damage.

While laboratory results tend to indicate that antivenin reduces local tissue injury when given soon after the snakebite, we feel the high complication rate associated with the antivenin does not justify its routine use in all circumstances. For systemic involvement, however, there is little question that antivenin seems to ameliorate the effects of envenomation. For this reason we use antivenin if and only if systemic involvement is present.

The question was raised regarding our rate of anaphylaxis. An article by Jurkovitch in the *Journal of Trauma* reported that 23% of his patients demonstrated an acute hypersensitivity response and anaphylactic shock, and 50% had serum sickness. Another paper reported an overall complication rate of 29%. Our numbers are consistent with the literature.

Dr. Pennell asked if we are seeing patients who are bitten on more than one occasion. We are. One of the first patients I treated was seen in the emergency room for anaphylactic shock. This was his third bite at a rattlesnake roundup, and this time he developed a severe hypersensitivity reaction to the snake venom. No antivenin had yet been given.

Dr. Baker asked how much antivenin we give. We recommend 5 to 10 vials at first, to be titrated to clinical response.

Dr. Burch asked if we use any blood products in the patients treated with antivenin. We used a total of 9 units of fresh frozen plasma and 6 units of packed red cells to treat envenomation associated coagulopathies and bleeding in our patients. We feel the danger of AIDS and hepatitis associated with the transfusion of blood products outweighs the morbidity associated with antivenin, therefore, decreasing or avoiding the use of blood products by using antivenin is advantageous to the patient.

Thank you for the opportunity to present our data for discussion.

Limb Salvage *Versus* Traumatic Amputation

A Decision Based on a Seven-part Predictive Index

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In severe traumatic injuries to the lower extremity, it is often a difficult decision to attempt heroic efforts aimed at limb salvage or to amputate primarily. To answer this question, the authors performed a 5-year review of 70 limbs in 67 patients. Patients were identified as presenting with major lower extremity trauma and an associated arterial injury. Nineteen (27%) of the 70 limbs were amputated. Limb salvage was not related to the presence or absence of shock and order of repair (orthopedic or vascular). No statistical difference was noted between the time of injury to operative repair in either the amputated or limb salvage group. Limb salvage was related to warm ischemia time and the quantitative degree of arterial, nerve, bone, muscle, skin, and venous injury. A limb salvage index (LSI) was formulated based on the degree of injury to these systems. All 51 patients with an LSI score of <6 had successful limb salvage ($p < 0.001$). All 19 patients with an LSI score of 6 or greater had amputations ($p < 0.001$). Although statistics cannot replace clinical judgment, this index can be a valuable objective tool in the evaluation of the patient with a severely traumatized extremity.

SEVERE TRAUMATIC INJURIES to the lower extremities have proven to be a profound challenge to the surgeon. With the high incidence of multiple systems involved (integument, nerve, bone, and vascular structures), these injuries require a multidisciplinary approach for appropriate management. With multiple surgical specialties represented in the care of these patients, the General/Trauma surgeon usually assumes the role of team leader. Complex decisions inevitably center around whether to attempt heroic efforts aimed at limb salvage or to proceed with primary amputation. Ongoing advances in on-scene trauma management, vascular reconstruction, microsurgical techniques, skeletal fixation, antibiotic therapy, and air ambulance systems have frequently led to more aggressive attempts at limb salvage in an otherwise doomed extremity. Sometimes "successful" reconstruction takes place, only for the patient to have severe functional deficits that ultimately lead to secondary amputation. This may not occur until months after exhaustive efforts by both patient and surgeon to save a limb. The debts incurred by these patients may be overwhelming, and financial obligations may never be met.

The objective of this study was to identify variables that may ultimately influence the outcome of a severely traumatized extremity with arterial compromise. This presumably would assist the surgeon in the initial decision-making process about whether to pursue extensive reconstruction efforts.

Patients and Methods

During a 5-year period from 1985 to 1990, 67 patients presented to Erlanger Medical Center, Chattanooga, Tennessee with 70 limbs having sustained major lower extremity arterial injury. Of the 70 limbs, 51 (73%) were salvaged and 19 (27%) sustained either primary (11), secondary (6), or functional (2) amputation. A limb was designated as a functional amputation if successful revascularization and wound healing occurred only to have a useless, nonfunctional extremity without weight-bearing ability, and with absence of motor and sensory function. The reasons for failure were analyzed in those limbs for which limb salvage was attempted, as well as the extent of injury in those limbs for which primary amputation was performed.

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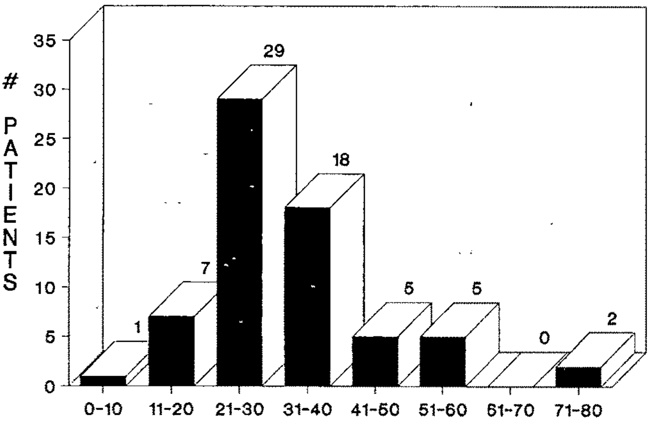

FIG. 1. Age of patients at time of accident (in years).

The average age of patients in this series was 31.9 years (range, 9 to 76 years) (Fig. 1). The mean age of those that required amputation was 33.5 years (range, 9 to 76 years), with one patient having bilateral amputations. There were 50 male and 17 female patients in the study group. The mechanisms of injury and amputation rates are listed in Table 1.

Pedal pulse deficits were documented in 36 limbs on arrival to the emergency room. Eighteen patients presented in shock, with a systolic blood pressure less than 90 mm Hg on arrival to the emergency room. Bone injuries were present in 51 limbs, muscle injuries in 57 limbs, and integument injuries in all limbs. Concomitant venous injury was present in 35 limbs. Nerve injuries were identified in 31 limbs. The mean interval from injury to the initiation of surgical intervention for the limb salvage group was 4.6 hours; in the amputated group, 5 hours. Combined vascular and orthopedic repair was undertaken in 29 limbs. Fasciotomy was performed in 22 patients.

This study specifically excludes limbs that were amputated in the field. The indications for reimplantation of these limbs has been established.[1,2] When appropriate, data was submitted to statistical analysis using the Fisher's exact probability test, chi square analysis, and Student's t test.

TABLE 1. *Mechanism of Injury and Amputation Rates*

Type	No. Limbs	Salvaged	Amputated
Total Blunt	35	17 (49%)	18 (51%)
MVA	21	13 (62%)	8 (38%)
Fall	3	2 (67%)	1 (33%)
Avulsion	4	1 (25%)	3 (75%)
Crush	7	1 (14%)	6 (86%)
Total Penetrating	35	34 (97%)	1 (3%)
HVGSW	3	2 (67%)	1 (33%)
LVGSW	21	21 (100%)	0
SGW	3	3 (100%)	0
Stab	6	6 (100%)	0
Laceration	2	2 (100%)	0

MVA, motor vehicle accident; HVGSW, high-velocity gunshot wound; LVGSW, low-velocity gunshot wound; SGW, shot gun wound.

TABLE 2. *Injury Level, Salvage, and Amputation Rates*

Artery	No. Injuries	Salvage	Amputation
Common femoral	1	1 (100%)	0
Superficial femoral	21	15 (71%)	6 (29%)
Profunda femoris	3	3 (100%)	0
Popliteal	17	11 (65%)	6 (35%)
Infrapopliteal	29	22 (76%)	7 (24%)

Results

Injuries were seen in the common femoral (1), superficial femoral (21), profunda femoris (3), popliteal (17), and infrapopliteal (29) arteries. One patient had injuries to both popliteal and infrapopliteal vessels. The level of injury, limb salvage, and amputation rates are shown in Table 2.

Thirty-six of seventy patients had documented pedal pulse deficits on arrival to the emergency room. Twenty-one (58%) limbs were successfully revascularized and salvaged; 15 (42%) limbs were amputated. Two of the fifteen amputated limbs had prolonged ischemia; one greater than 6 hours, the other greater than 15 hours. Eighteen (26%) patients presented in shock, with six patients ultimately requiring amputation, and 12 having successful limb salvage ($p > 0.05$). Thirty limbs presented with documented sensory or motor deficits in the emergency room. Operative findings showed 31 nerve injuries, including sciatic (10), combined common peroneal and tibial (11), tibial alone (2), common peroneal alone (5), and femoral (3) (Table 3). All 19 limbs amputated had nerve injuries, including sciatic (7), combined common peroneal and tibial (10), and common peroneal alone (2).

Bone injuries were identified in 51 limbs, 22 of which were of the Gustilo type III-C. This type of injury was described in 1984 as having an open unstable fracture, massive soft-tissue trauma, gross contamination, periosteal stripping, and associated vascular injury requiring surgical repair.[3] Thirteen (59%) of the 22 type III-C frac-

TABLE 3. *Nerve Injury, Salvage, and Amputation Rates*

Nerve	No. Injuries	Salvaged	Amputation
Sciatic	10	3 (30%)	7 (70%)
Combined common peroneal and posterior tibial	11	1 (9%)	10 (91%)
Posterior tibial	2	2 (100%)	0
Common peroneal	5	3 (60%)	2 (40%)
Femoral	3	2 (67%)	1 (33%) Associated sciatic nerve injury

TABLE 4. *Associated Injuries—Amputated*

Type of Injury	Amputations (n = 19)
1. Vascular-arterial	19 (100%)
2. Vascular-venous	16 (84%)
3. Bone	19 (100%)
Type III-C	13
4. Nerve	19 (100%)
5. Muscle	19 (100%)
6. Ischemia > 6 hours	2 (11%)
7. Integument	19 (100%)
Requiring STSG or flap	17

STSG, split-thickness skin graft.

tures were amputated. All patients with a type III-C fracture and amputation had associated complete disruption of either the sciatic or tibial nerve ($p < 0.001$). Three amputated limbs had segmental bone loss greater than 3 cm, two had closed fractures, and a single patient had an open comminuted displaced fracture. In the limb salvage group, 25 patients presented with open fractures (type III-C [9]), and seven patients had closed fractures (two posterior knee dislocations). None of the patients with a type III-C fracture in this group had an associated nerve injury. Muscle injuries were present in 57 limbs. All extremities evidenced skin loss, with 26 limbs injured to the extent that split-thickness skin graft or flap repair would be required. Of those 26 limbs, nine were salvaged.

The mean time of injury to operative repair was 4.6 hours for the limb salvage group, and 5 hours for the amputated group ($p > 0.05$).

Combined vascular and orthopedic repair was undertaken in 29 limbs. Vascular repair preceded orthopedic repair in 23 patients (limb salvage, 19; amputated, four). Orthopedic repair preceded vascular repair in six patients (limb salvage, five; amputated, one). Those differences were not statistically significant ($p > 0.05$) Fasciotomy was performed in 22 patients (limb salvage, 19; amputated, 4). Concomitant venous injury was present in 35 limbs, of which primary amputation occurred in 8, and secondary or functional amputations in 8. Four of the eight patients with secondary or functional amputations had associated venous injury (three repaired, one ligated). Of those patients in whom limb salvage was achieved, eight patients had ligation of infrapopliteal veins with no long-term sequelae. Twelve patients had either popliteal or superficial femoral venous injury, and all were repaired except four (one popliteal, and three femoral). Only three had mild edema at discharge (femoral vein group).

TABLE 5. *Associated Injuries—Limb Salvage*

Type of Injury	Limb Salvage (n = 51)
1. Vascular-arterial	51 (100%)
2. Vascular-venous	19 (37%)
3. Bone	32 (63%)
Type III-C	9
4. Nerve	12 (23%)
5. Muscle	38 (75%)
6. Ischemia > 6 hours	8 (16%)
7. Integument	51 (100%)
Requiring STSG or flap	9

STSG, split-thickness skin graft.

Associated injuries in the salvaged and amputated groups are shown in Tables 4 and 5.

TABLE 6. *Limb Salvage Index Scoring System*

Location	Points	Extent of Injury
Artery	0	Contusion, intimal tear, partial laceration or avulsion (pseudo-aneurysm) with no distal thrombosis and palpable pedal pulses; complete occlusion of one of three shank vessels or profunda.
	1	Occlusion of two or more shank vessels, complete laceration, avulsion or thrombosis of femoral or popliteal vessels without palpable pedal pulses.
	2	Complete occlusion of femoral, popliteal, or three of three shank vessels with no distal runoff available.
Nerve	0	Contusion or stretch injury; minimal clean laceration of femoral, peroneal, or tibial nerve.
	1	Partial transection or avulsion of sciatic nerve; complete or partial transection of femoral, peroneal, or tibial nerve.
	2	Complete transection or avulsion of sciatic nerve; complete transection or avulsion of both peroneal and tibial nerves.
Bone	0	Closed fracture one or two sites; open fracture without comminution or with minimal displacement; closed dislocation without fracture; open joint without foreign body; fibula fracture.
	1	Closed fracture at three or more sites on same extremity; open fracture with comminution or moderate to large displacement; segmental fracture; fracture dislocation; open joint with foreign body; bone loss < 3 cm.
	2	Bone loss > 3 cm; Type III-B or III-C fracture (open fracture with periosteal stripping, gross contamination, extensive soft tissue injury-loss).
Skin	0	Clean laceration, single or multiple, or small avulsion injuries, all with primary repair; first degree burn.
	1	Delayed closure due to contamination; large avulsion requiring STSG or flap closure. Second and third degree burns.
Muscle	0	Laceration or avulsion involving a single compartment or single tendon.
	1	Laceration or avulsion involving two or more compartments; complete laceration or avulsion of two or more tendons.
	2	Crush injury.
Deep Vein	0	Contusion, partial laceration, or avulsion; complete laceration or avulsion if alternate route of venous return is intact; superficial vein injury.
	1	Complete laceration, avulsion, or thrombosis with no alternate route of venous return.
Warm Ischemia Time	0	<6 hours
	1	6–9 hours
	2	9–12 hours
	3	12–15 hours
	4	>15 hours

STSG, split-thickness skin graft.

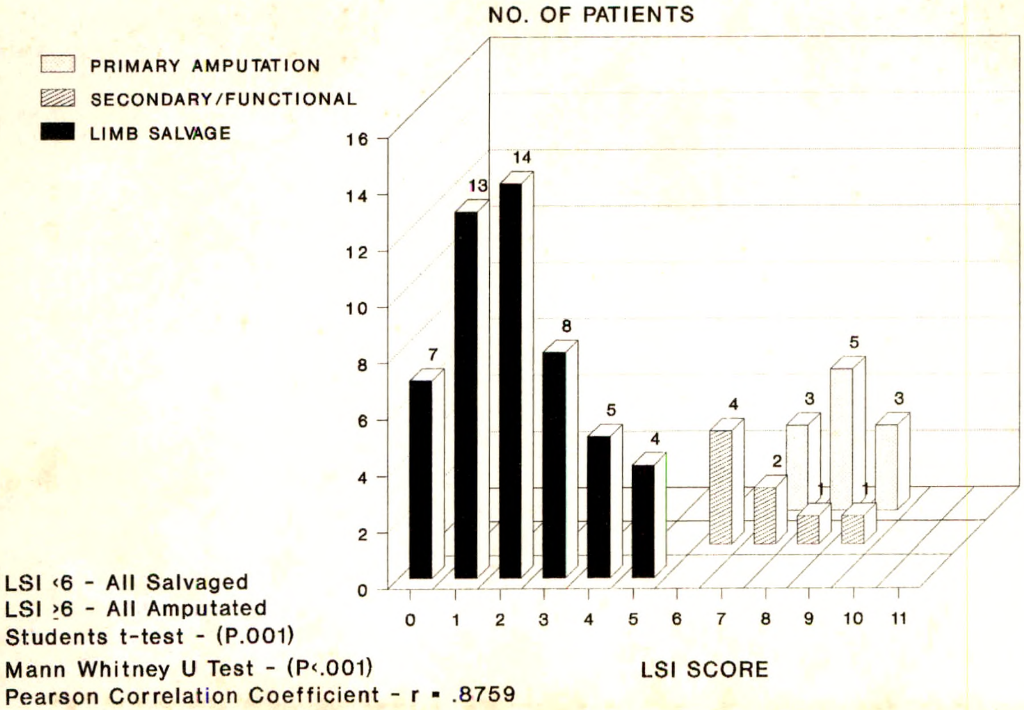

FIG. 2. Limb salvage index distribution.

A limb injury index was developed based on skin injury (0 to 1 points), muscle injury (0 to 2 points), bone injury (0 to 2 points), nerve injury (0 to 2 points), vein injury (0 to 1 points), arterial injury (0 to 2 points), and length of warm ischemia time (0 to 4 points) (Table 6).

Seventy limbs were scored with the limb injury index. All patients with scores less than 6 had limb salvage achieved. All 19 in the amputated group had scores of 6 or greater (Student's t test: $t = -14.97$ [$p < 0.001$], Mann-Whitney U Test [$p < 0.001$], Pearson correlation coefficient [$r = 0.8759$] [Fig. 2]). Three cases are presented to further illustrate the use of the limb salvage index.

Case Reports

Case 1

A 19-year-old man involved in a hunting accident was shot with a 30-06 rifle in the right lower extremity at the level of the trifurcation. The patient had massive soft tissue loss, avulsion of the posterior tibial and common peroneal nerves, transection of the trifurcation vessels with thrombosis of the distal popliteal artery, transection of two tibial veins, and an open-comminuted displaced fracture of the proximal tibia and fracture through the femoral condyle (Fig. 3). On arrival to the emergency room, warm ischemia time was documented to be 8 hours 15 minutes. The patient was taken to the operating room, where a multidisciplinary team approach was used. Revascularization of the foot was achieved, external fixation of fractures accomplished, and wounds were initially packed open because of contamination. The patient remained hospitalized for 52 days. He underwent surgery on four occasions by the orthopedic service, and on two occasions by the plastic surgery service, the last of which was a flap closure of his wounds. Over the next 18 months, the patient was hospitalized on four occasions for bony non-union, development of osteomyelitis, and partial flap failure. Throughout this period, the patient had what is designated as a functional amputation.

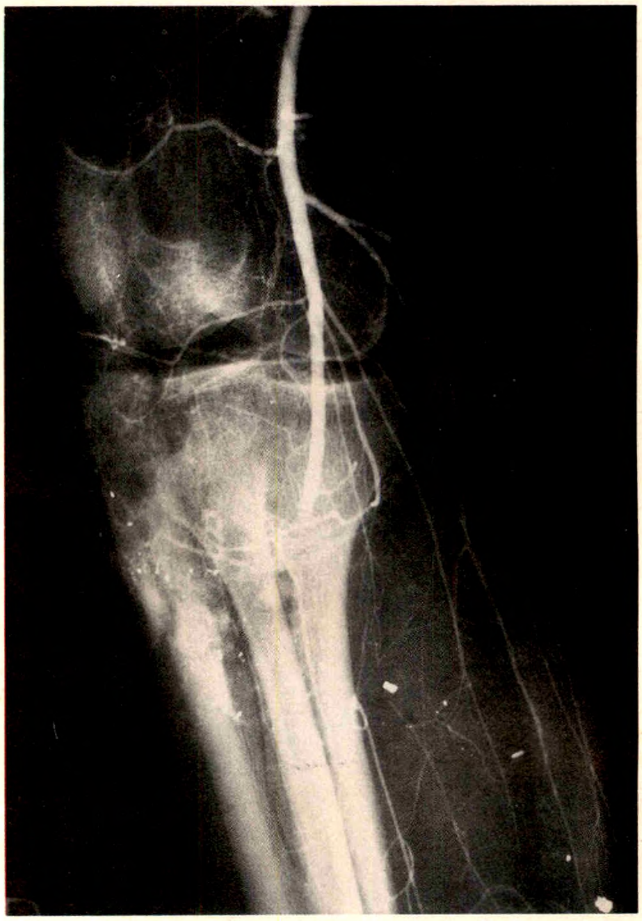

FIG. 3. Rifle injury resulting in a complete occlusion of the distal popliteal artery with collateral flow around the knee. Comminuted-displaced fracture of the proximal tibia. Note the presence of soft-tissue air.

Approximately 20 months after initial injury, the patient was returned to the operating room and underwent an above-knee amputation because of bony non-union and an insensate foot with absence of motor function. The patient was ambulating on a prosthesis in 2 months, and had returned to work in 3 months. His limb salvage index score was 8.

Case 2

A 21-year-old woman involved in an industrial accident was gored by a forklift through the right thigh, resulting in a massive degloving-type soft tissue injury, a comminuted open femur fracture, and an avulsion of her superficial femoral artery and vein (Figs. 4 and 5). Warm ischemia time was less than 6 hours. She was also noted to have a right inferior ramus fracture of the pelvis. The patient was taken to the operating room, where a multidisciplinary team approach was used. She had flow restored to the distal extremity initially with indwelling vascular shunts and stabilization of the femur fracture with external fixation. The sciatic nerve was explored and noted to be contused but intact. A reverse saphenous vein graft was used both for the arterial and the venous repair. The graft was covered and the wound was left open. The patient was returned to the operating room on three occasions for irrigation and debridement. The third operation included internal fixation of the femur, reapproximation of soft tissues, and a split-thickness skin graft. The patient was hospitalized for 36 days, and ambulated with a walker on hospital day 30. Seven months after her initial hospitalization, a follow-up examination showed that all wounds had healed. She was ambulating without assistance and had returned to nursing school. The patient's limb salvage index score was 5.

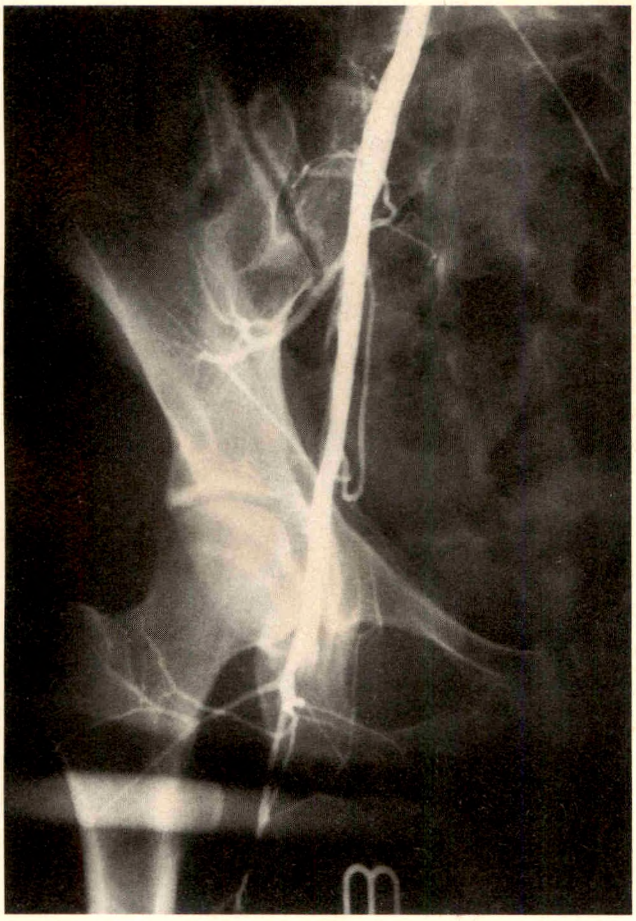

FIG. 4. Avulsion of the superficial femoral and profunda femoris arteries as a result of being gored by a forklift through the proximal thigh.

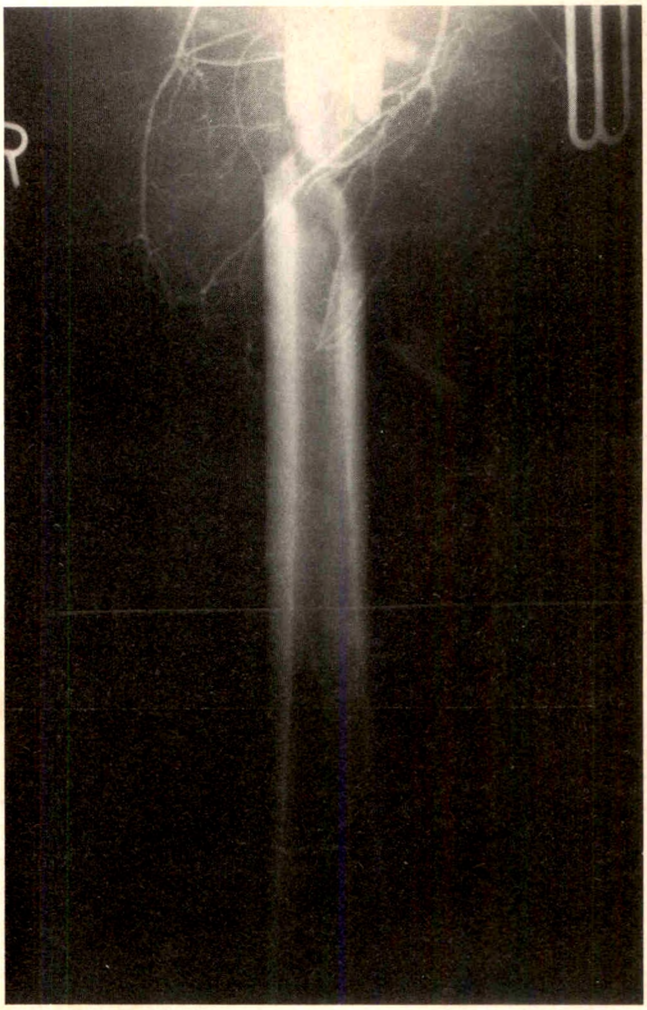

FIG. 5. Arteriogram showing absence of flow through the superficial femoral artery with sparse collateralization. Proximal displaced femur fracture with bone fragment noted distal to the fracture site.

Case 3

A 15-year-old girl sustained a crush injury to the left lower extremity and distal tibial region when she was hit by a truck. She presented with a partial amputation of the left lower extremity with segmental bone loss of approximately 5 cm, avulsion of the common peroneal and posterior tibial nerves, avulsion of all infrapopliteal vessels, a degloving injury to the skin, and crush injury to the muscle with tendon involvement at the ankle (Fig. 6). She was 12 weeks pregnant. Orthopedic and plastic surgery attempted a combined repair. She had repair of the posterior tibial neurovascular bundle using microsurgical techniques, including bone shortening with application of an external fixator (Fig. 7). A fasciotomy of the foot was performed. Her wounds were packed open, and she remained in the intensive care unit for 5 days. She returned to surgery on three occasions for irrigation and debridement. The limb was declared nonviable by the fifth postoperative day. She underwent a below-knee amputation on the seventh postoperative day, and was discharged 4 days later. She was ambulating on a prosthesis 2 months later. The patient's limb salvage index score was 9.

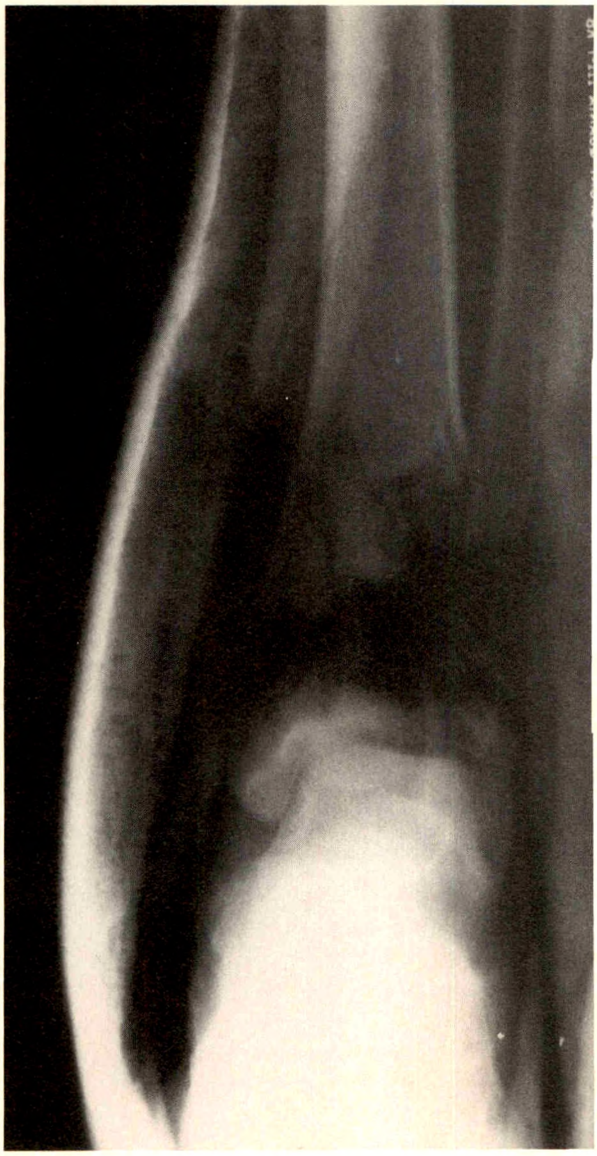

FIG. 6. Splint has been applied; however note the comminuted fracture of the distal tibia with marked bone loss just proximal to the ankle.

Discussion

In developing the limb loss index, we did not want to burden the surgeon with one more scale to use in the assessment of a trauma patient. We believe, however, that we have developed a guide for accurately evaluating trauma to the lower extremity, taking into consideration the systems involved and the degree of severity of injury to these systems. This index can assist the surgeon in making a decision as to the viability of an injured limb and the likelihood of success in salvaging the limb.

Amputation rates associated with traumatic arterial injuries range from 20% to 50%.[4–7] In this series the amputation rate in severely traumatized extremities was 27%. Blunt injuries carried a higher amputation rate, with 18 (51%) of 35 limbs amputated, as compared with penetrating trauma, where only one (3%) of 35 limbs required amputation ($p < 0.001$). Of those patients with blunt injuries, the most severe were crush/avulsion injuries, in which nine (82%) of 11 patients ultimately had limbs amputated ($p < 0.03$). Of the variables identified to predict limb salvage, there was no difference between the amputee group and limb salvage group when we looked at the presence or absence of shock, the time of injury to operative repair, or the order of vascular and orthopedic repair. We did find that the absence of pedal pulses on arrival, in association with the severe soft tissue, bone, and nerve injuries seen in these extremities, was more indicative of a poor outcome than when pulses were present with this type of injury.

Only one patient in this series presented with a pedal pulse deficit and prolonged ischemia for more than 12 hours. This patient ultimately required amputation after limb salvage was attempted. To save an extremity, it is imperative that there be early recognition of arterial injury. Miller and Welch[8] have documented in a canine model a salvage rate of greater than 90% with ischemic periods

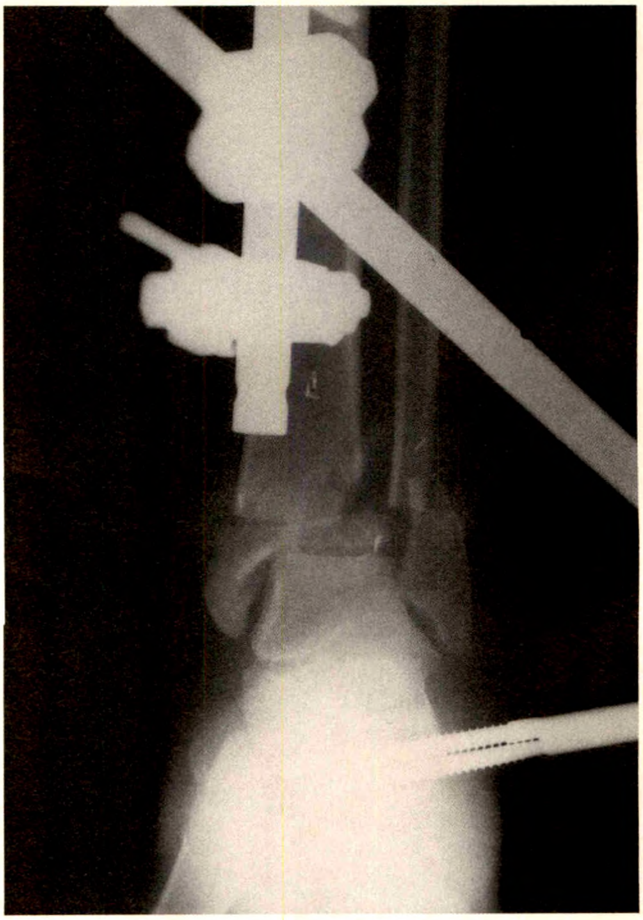

FIG. 7. The bone has been shortened and external fixator applied to stabilize the ankle.

of less than 6 hours. His limb salvage rates were less than 50% with ischemia of greater than 12 hours. The importance of this variable in the traumatized extremity and its potential for poor outcome with prolonged ischemia is emphasized in our limb salvage index (0 to 4 points).

Peripheral nerve injuries were present in all patients in the amputated group. Ninety-five per cent of limbs that were amputated had complete transection or avulsion of the sciatic, tibial, or peroneal nerve. The association of permanent nerve deficits with ultimate amputation is well documented.[6,9-15] The most severe deficits are those associated with sciatic injuries at the level of the hip with denervation of the hamstrings, tibial, and common peroneal nerves, leading to 100% limb disability.[12] The next most severe is a complete tibial nerve injury at the level of the knee, which is associated with a 60% to 70% limb disability.[12] Recognition of a posterior tibial nerve injury is particularly important, as it leads to the loss of plantar sensation, paralysis of intrinsic foot musculature, and frequently to neuropathic ulcerations.[12-15]

Severe bone injuries to the lower extremities have devastating consequences. In 1969 Gustilo designated compound fractures as types I, II, and III.[16] In 1984, Gustilo et al.[3] further subdivided type III injuries into III-A, III-B, and III-C, based on the injury and the order of worsening prognosis. The severity of a type III-C fracture alone is reflected by amputation rates that range from 42% to 78%.[3,17]

Twenty-two limbs in this series had Type III-C fractures, 13 (59%) of which ultimately required amputation, and nine (41%) of which were salvaged. The difference in amputation rates was a function of associated nerve injury with this severe type of fracture. All patients undergoing amputation with a type III-C fracture had complete disruption of either the sciatic or tibial nerves. This emphasizes the potential for poor outcome with these types of injuries, especially in combination with extensive nerve injury. Absolute indications for primary amputation with type III-C injuries have been proposed by Lange et al.[18] and supported by Caudle and Stern.[17] This series does support the indication for primary amputation of type III-C injuries in association with irreparable tibial nerve injury.

The timing of vascular repair and stabilization of various orthopedic injuries remains controversial. Many authors have stressed the importance of initial fracture stabilization followed by vascular repair to prevent possible disruption of a vascular anastomosis during fracture stabilization.[19-21] Others have advocated the use of shunts for peripheral arterial injuries to reestablish blood flow to the distal extremity, followed by fracture stabilization and then definitive vascular repair.[19,22-24] Although our study did not show a difference in outcome with regard to the order of repair, it is our senior author's recommendation that one proceed with vascular repair or shunting to reestablish perfusion to the affected extremity before fracture stabilization. The general/vascular surgeon should remain involved in the procedure to protect or revise the vascular repair and assure adequate soft tissue coverage of the repair after fracture stabilization.

Perry et al.[25,26] have clearly defined the pathophysiology of compartment syndromes. The indications for fasciotomy are well documented in the literature.[27-29] In this series fasciotomy was performed in 17 (33%) of 51 patients who had limb salvage achieved and in five (63%) of eight patients with either secondary or functional amputation. Although these numbers appear small, they do not include the majority of patients who presented with self-induced fasciotomy as a result of their injury. Vitale et al.[30] have shown fasciotomy to be a safe adjunctive procedure in limb salvage with very little morbidity. All extremity injuries of this magnitude should have some type of compartmental release to allow for expansion of the respective tissues.

Many stress the inherent risk of amputation with an arterial injury below the knee.[31-33] Howe et al.[31] emphasized this in their system for scoring arterial injuries, with an amputation rate of 80%. A cumulative amputation rate of 18% has been noted in various reports of infrapopliteal injuries.[32,34-37] In this series the risk of amputation after infrapopliteal injury closely approximates that previously reported, with seven (24%) of 29 infrapopliteal injuries ultimately leading to amputation. We did find, in those seven extremities with infrapopliteal vascular injuries, multiple associated injuries. We found that the degree of total injury to the extremity correlates with the potential for amputation to a greater extent than did the level at which arterial injury occurred alone.

Summary

Based on the analysis of 70 lower extremity injuries involving multiple systems, a limb salvage index was derived. By careful initial and operative evaluation of vascular, nervous, bone, soft tissue, and venous systems, as well as warm ischemia time, it was possible to more closely predict limb salvage.

Amputation, although never the primary goal of the physician, may well be the procedure of choice in some cases. By proceeding with primary or early secondary amputation, it is often possible to quickly return a healthy productive individual back to society rather than have the patient suffer from a chronic nonfunctional state.

Although surgeons tend to become enamored of technical advances in the provinces of the surgical subspecialties, we must remain cognizant of the overall long-term result to the patient. The patient may be better served with a primary amputation, as failure in this setting may induce serious psychological and financial hardships on the patient and his family.

Absolute indications for amputation from this study include (1) a patient with a limb salvage index of 6 or greater ($p < 0.001$), and (2) a patient with Gustilo type III-C fracture with associated nerve injury ($p < 0.001$). A relative indication is a patient with a severely traumatized extremity and associated sciatic or tibial nerve injury.

Numbers cannot replace clinical judgment. This index can be a valuable objective tool, however, in the evaluation of the patient with a severely traumatized extremity. By more accurately identifying the patient who would most benefit from "heroic" multispeciality efforts, the surgeon can assure a more proper outcome and appropriate use of resources.

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DISCUSSIONS

DR. MALCOLM PERRY (Nashville, Tennessee): This is obviously an extremely difficult decision. Most of us feel that it's possible to save the majority of limbs; and those of us in vascular surgery almost always can revascularize the limb if we are willing to accept some limb shortening.

The average age of these patients was 31 years; therefore one would anticipate, for the most part, that the vascular system could be revascularized. There should not be a great deal of atherosclerosis.

Early in my limb replantation experience I made the mistake of replanting a lower limb in a patient who had it blown off by an explosion of acetylene and oxygen. The limb survived, but he ended up with an anesthetic post and eventually, some years later, it was necessary to do an amputation. It was very difficult for him, for the family, and for me.

What Dr. Russell and his colleagues have brought to us is a reflection of what Ben Eiseman said sometime ago: we need to assess the extent of the trauma and avoid prolonged debilitating physical and financial burdens on the family and the patients.

I worry about the basis of the scoring system. It is qualitative rather than quantitative. It is quite clear that major motor nerve injury, and perhaps even more important, the failure to retrieve the protective reflexes, leaving an insensate extremity that cannot be protected from harm, leads to a bad result. The combination of bone and nerve was predictive in this study.

The amount of soft-tissue damage and the loss of integument are important, but it is hard to qualitate those things. Despite the good basis for the prediction, there are no hard data yet.

I have other concerns: 'Will the busy surgeon spend time with a complex scoring system?' It appears that you have identified several predictors, particularly the combination of major bone and nerve, which might allow you to streamline the system. I must confess that I have some doubt about scoring indexes, although the trauma index has proved to be useful. I think that this needs to be studied. I would hope that you could streamline it a bit, because at present I'm not sure that most people would use it.

DR. DAVID RICHARDSON (Louisville, Kentucky): As our colleagues in orthopedic and plastic surgery have become more skilled and aggressive, as they mention, we often find ourselves as team leaders in a position of not knowing when to stop trying to save an extremity. I think the authors' method, whether we use it completely *in toto*, certainly lends credence to the fact that there are extremities that simply can not be saved in a useful way.

In 1986 we reported on 37 amputations after trauma and used a four-point grading system to dictate the need for early amputation. And many of the points are very similar to what the authors use. We found in our grade 1 and grade 2 injuries, which basically would give you a number less than six, using their system, that only one amputation was required—and that was for a delayed infection—of about 70 patients treated in those categories.

However in our grade 4 injuries, using the classification system there, which included vascular injury, bony injury, and either a major soft-tissue or nerve injury, we had 17 patients who required completion amputation or had an immediate amputation.

More importantly, though, of the 13 extremities with which we went to great lengths using a multimodality approach to try to save the extremity, 11 of those were lost at some point, including several delayed amputations for nerve injuries, despite what, to look at it, seemed to be a fairly good salvage.

All of our patients with nerve injuries of any significant degree eventually required amputations.

Are there some potential combinations of these six points where limbs might still be salvageable? In looking at it, I thought you could possibly come up to six and still have some extremities that might be worth saving.

I also have a comment about the point you made about nerve injury. If you have a total transection of either sciatic or posterior tibial nerve, especially in combination with multiple other injuries, is that extremity really worth the significant effort? And then we still try to be very aggressive in patients who will require an above-knee amputation, simply because I think that our ability to rehabilitate that patient is not so good. Does the level of amputation enter into the decision about whether to move to an early amputation?

DR. RICHARD FIELD (Centerville, Mississippi): We are seeing more and more trauma. A limb salvage index is something that will be useful to us, something we can put on our emergency room doors, we can put in our heads, and it will give us some idea or some standard to go by to salvage limbs.

You know, in days gone by, the question would be 'Can we or can we not save this extremity?' And a lot of times it was—most of the time it was a relatively easy problem. But now we can save nearly every extremity that we see.

As David Richardson just said, we have this multimodality approach and we can save every limb up in the 90th percentile. But the question is, and I turn your focus for a minute, what about the philosophical approach. Are we really doing anything to help this individual? And I think all of the discussants, including Bill Russell, are all questioning the quality of limb and the quality of gait and the quality of life with which we are leaving this individual.

One of the dangerous problems that I would direct your attention to now is the multimodality, multispecialty approach. When we get the neurosurgeons, the orthopedists, the general surgeons, and the vascular surgeons involved, who will decide if this limb, which we can obviously save, will be a worthwhile extremity for the individual or will it become a painful financial and psychological burden for the remainder of the patient's life, who would have been better served by an amputation.

DR. W. L. RUSSELL (Closing discussion): Dr. Perry I agree this issue certainly needs more study. We are continuing to look at this in a more perspective manner, and I think there are some areas in which we can streamline our index. This really was our attempt with a large enough patient base to try to make some sense of this group of patients.

Dr. Richardson I am sure there is some potential combination that would achieve a score of six. The major nerve injury seems to be a determining factor. In the absence of such, ischemia greater than 6 hours, for example, could produce a total of six other systems injured and still result in a salvage. In our particular group of 70 patients, we did not achieve that. We came very close. We had one patient who had a score of five and missed a six by 20 minutes on her warm ischemia time.

As far as the level of amputation, I think that there is no question but what a below-the-knee amputation is far preferable to an above-the-knee.

And in our group of patients, we had 11 below-knee amputations and six above the knee. An effort certainly should be made to maintain that joint, if at all possible.

Dr. Field we appreciate the insight you brought to us. We, too, agree that it is important to make a decision early. In talking to some of our rehabilitation experts, they tell us that it requires about 15% less energy, for example, for a patient to ambulate with a prosthesis than it does to ambulate with crutches and a functionless extremity.

So there are a few other folks who are looking at this as well.

I'd like to thank David Sailors who assisted significantly in the preparation of this paper.

Prehospital Hypertonic Saline/Dextran Infusion for Post-traumatic Hypotension

The U.S.A. Multicenter Trial

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The safety and efficacy of 7.5% sodium chloride in 6% dextran 70 (HSD) in posttraumatic hypotension was evaluated in Houston, Denver, and Milwaukee. Multicentered, blinded, prospective randomized studies were developed comparing 250 mL of HSD *versus* 250 mL of normal crystalloid solution administered before routine prehospital and emergency center resuscitation. During a 13-month period, 422 patients were enrolled, 211 of whom subsequently underwent operative procedures. Three hundred fifty-nine patients met criteria for efficacy analysis, 51% of whom were in the HSD group. Seventy-two per cent of all patients were victims of penetrating trauma. The mean injury severity score (19), Trauma Score plus Injury Severity Score (TRISS) probability of survival, revised trauma scores (5.9), age, ambulance times, preinfusion blood pressure, and etiology distribution were identical between groups. The total amount of fluid administered, white blood cell count, arterial blood gases, potassium, or bicarbonate also were identical between groups. The HSD group had an improved blood pressure ($p = 0.024$). Hematocrit, sodium chloride, and osmolality levels were significantly elevated in the Emergency Center. Although no difference in overall survival was demonstrated, the HSD group requiring surgery did have a better survival ($p = 0.02$), with some variance among centers. The HSD group had fewer complications that the standard treatment group (7 *versus* 24). A greater incidence of adult respiratory distress syndrome, renal failure, and coagulopathy occurred in the standard treatment group. No anaphylactoid nor Dextran-related coagulopathies occurred in the HSD group. Although this trial demonstrated trends supportive of HSD in hypotensive hemorrhagic shock patients requiring surgery, a larger sample size will be required to establish which subgroups of trauma patients might maximally benefit from the prehospital use of a small volume of hyperosmolar solution. This study demonstrates the safety of administering 250 mL 7.5% HDS to this group of patients.

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INTRAVENOUS INFUSION HAS been the mainstay of prehospital and emergency center management of postinjury hypotension for the last half of this century.[1-12] With the development of systems of rapid prehospital transportation and trauma centers, however, the type, volume, and even value of prehospital fluid resuscitation have been challenged during the last decade.[13-16] In the civilian urban setting with short transport times and in the military setting with need to limit volume, weight, and amount of supplies and resupply routes, logic encourages development of a smaller-volume, but equal (or even superior) fluid resuscitation regimen. Smaller-volume infusions of hypertonic solutions have been the subject of both laboratory and clinical studies demonstrating increased plasma volume, increased cardiac work, increased microcirculation and decreased splanchnic resistance.[17-39] The favorable results of pilot studies evaluating 7.5% sodium chloride in 6% dextran 70 have warranted a multicentered study enlisting a concurrent large number of patients with post-traumatic hypotension to prove the safety and value of such solutions.[41-45] The purpose of the study reported herein was to evaluate the role of such solutions within the confines and limitations of the experimental design.

Methods

Experimental Design

This was a multicenter, double-blind, randomized study in which hypotensive trauma patients received 250 mL

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of either the treatment solution (7.5% NaCl in 6% dextran 70) or a standard isotonic resuscitation solution (Plasma-Lyte®/Lactated Ringer's/saline) as initial intravenous infusion. As with previous prehospital resuscitation studies, field entry criterion of an initial blood pressure equal to or less than 90 mmHg systolic was used.[46-58] Three centers (Ben Taub General Hospital in Houston, Denver General Hospital, and Milwaukee County Medical Complex) and a total of 28 paramedic-staffed ambulances participated. Multiple centers were required because no single center could enroll a sufficient number of patients within the planned time span nor assure that blunt and penetrating injury would be observed with nearly equal frequency. All three study centers were verified as Level I Trauma Centers by the American College of Surgeons Committee on Trauma and were functioning as the regional trauma facility in their respective metropolitan areas. These centers were selected not only because they had previously demonstrated the ability to provide standardized prehospital advanced life support, but also because of well-documented standardized in-hospital trauma care. Each of the prehospital and hospital trauma services are under the direction of one of the co-investigators. Milwaukee County Medical Complex started recruiting patients approximately 3 months after the Houston and Denver sites. Besides altitude and some minor differences in transport times, the only other difference among centers was the choice of 'routine' prehospital and emergency center resuscitative fluids. Ben Taub Hospital used Plasmalyte A (Ringer's Acetate); Denver General Hospital used normal saline, and Milwaukee County Medical Complex used Ringer's Lactate. The study began in October 1987 and was concluded on November 19, 1988, with the enrollment of 424 patients.

Patient Population

Paramedics at the scene identified and enrolled in the study patients who met the following inclusion criteria: (1) 16 years of age or older, (2) victim of penetrating or blunt trauma within the last hour before randomization, and (3) initial field systolic blood pressure of 90 mmHg or less.[46-58] Exclusions included (1) initial trauma score equal or less than 2, (2) revised trauma score equal or less than 1, (3) pregnancy, (4) history of seizures, coagulopathy, liver or renal disease, or (5) patients in whom medical antishock trousers were applied.

Patient Consent

The patient, next of kin, or agent, in requesting emergency medical services on behalf of the patient, requests that appropriate, standard resuscitation and treatment measures be undertaken. This action implies a consent to treat. The hypotensive patient, especially if obtunded, is in no condition to comprehend or accept traditional informed consent measures. In the time frame required, family members are often NOT present or in an appropriate setting to fully understand or comprehend study protocols, let alone provide an informed consent to routine treatment. Previous emergency medical service (EMS) and Trauma Center clinical studies have demonstrated the life-saving effect of invoking such implied consent when they rapidly administer both basic and advanced resuscitative measures, especially if those potentially valuable measures are added to already accepted methods. Such logic also has been applied to virtually all time-dependent prehospital, emergency center, and trauma center studies since the inception of the EMS concept in the early 1970s. Therefore because true informed consent cannot be obtained and because preclusion of the study for this reason would deny patients the benefit of a potentially life-saving effect, an agreement to study with the scrutiny of institutional review boards and risk-monitoring assessments was accepted in all three institutions.

Randomization/Technique of Blinding

The randomization and blinding techniques were designed so as not to delay accepted emergency treatment. Ambulances enrolled in this study were supplied with consecutively numbered 250-mL bags containing a sterile solution of either Ringer's lactate or 7.5% NaCl in 6% dextran 70 (2400 mOsm), supplied by Pharmacia (Piscataway, NJ). After initial vital signs were obtained, a 250-mL bag of fluid was administered. Pharmacia tagged each bag with a five-digit randomization code. A postcard with this number, the sequence number, case form booklet number, and a patient identifier supplied by each research center was sent to an independent research coordinator at the time of use. Wasted, broken, or discarded bags were identified and recorded. Neither the paramedics, emergency center doctors/nurses, surgeons, or the center investigators knew the bag contents until the end of the study, unless an adverse reaction mandated investigation.

End Points

Survival was the only primary end point and was assessed at 24 hours and 30 days (if possible). Secondary end points included: improvement in 24-hour physiologic status, reduced postinjury complications, decreased fluid volume resuscitation needs in the prehospital phase or in the emergency center, and safety of hypertonic saline/dextran solutions (in the volume given) with regard to seizures, anaphylactoid reactions, and coagulopathies.

Statistical Analysis

The Dixon Statistical Associates (Los Angeles, CA) were contracted to collate the composite data as it was received from the three centers. This firm participated in formu-

TABLE 1. *Summary of Epidemiologic Data*

Epidemiologic Condition	HSD n	HSD %	STD n	STD %
Etiology				
Penetrating	153	73	151	72
Blunt	54	26	57	27
Unknown	4	2	3	1
Race				
White	51	28	36	21
Black	71	39	77	44
Other	62	34	62	35
Males (% male)	184	83	175	85
	n	Mean ± SD	n	Mean ± SD
Age	182	34 ± 12	172	33.± 12
Injury severity score	184	19 ± 13	175	19 ± 15
TRISS (Prob surv)	171	0.84 ± 0.29	164	0.83 + 0.32
Revised trauma score				
Preinfusion	172	5.98 ± 1.61	165	5.93 + 1.75
Emergency center	149	7.43 ± 0.97	139	7.25 + 1.16

HSD, hypertonic saline/dextran treatment group; STD, standard treatment group; TRISS, Trauma Index and Injury Severity Score; Prob surv, probability of survival; SD, standard deviation.

lating the data collection instrument and the prestudy statistics to optimize the entry, as well as analyses and interpretation of collected data. The study was initially designed to enroll 700 patients, to detect a change of ± 0.10 from a mean 24-hour survival of 75% at a significance level of 0.05 and a power of 80%. This survival assumption of 75% in the control group was based on a similar study performed in an identical patient population.[38] Treatment groups were compared using demographic variables (age, sex, and race), ambulance response time, Revised Trauma Score, TRISS, Injury Severity Score, and vital signs. Survival functions estimated using life-table analysis were used to estimate 24-hour survivals. BMDP statistical software (Dixon Statistical Associates) was used for statistical computations. Descriptive statistics, t tests, chi square tests, analysis of variance, logistic regression, and survival analysis were performed using BMDP Programs. All probability values or any notation of statistical significance in this report were calculated independently by the Dixon Statistical Associates and the values cited came from their calculations.

Results

Patient Enrollment/Demographics

Four hundred twenty-four patients were enrolled; 204 from Ben Taub General Hospital (15 participating ambulance units); 132 from Denver General Hospital (7 ambulance units), and 88 from the Milwaukee County Medical Complex (6 ambulance units) (Tables 1 and 2). These 424 patients were 'intent to treat,' in other words, assigned a bag of treatment solution. The identification on two of the treatment bags was lost, and 63 patients were excluded from the 'efficacy' analysis because they (1) did not receive a full 250 mL of blinded treatment solution (36 patients), (2) were found retrospectively not to meet inclusion/exclusion criteria (17 patients), or (3) were not followed 24 hours or until death because of early transfer to another hospital (10 patients). The efficacy analysis is based on 359 patients (84.7% of the total patients 'intended to treat'). A separate analysis of the 'intent to treat' patients was made, and results did not differ from analysis of the 'efficacy' patients. The availability of the 'efficacy' patient's assessment of primary and secondary end points makes this group statistically complete and accurate.

Patient and Injury Characteristics

Seventy-two per cent of the patients suffered penetrating injury; of patients treated at Ben Taub General Hospital, 88% had penetrating wounds; whereas 55% treated at Denver General Hospital had penetrating injury (Table 2). This was a departure from the original research projection of more blunt trauma patients at the Denver and Milwaukee sites. Seventy per cent of the blunt injuries were from motor vehicle accidents, and 12% were from auto–pedestrian accidents and falls. Eighty-two per cent of the patients were men, 24% were white, 43% black, and 33% were Hispanic or Oriental. The average age was 34 years (Table 1). The average ISS was 19 in both groups, and the classic distribution of ISS for severely injured patients was similar among centers, indicating a similar patient inclusion mix (Table 3). The mean preinfusion revised trauma score was 7, and the mean preinfusion TRISS was 0.83 in both study groups, again demonstrating an almost identical patient mix. The mean probability of

TABLE 2. *Summary of Injury Data by Injury Type (Intent to Treat Patients)*

Study Site	HSD (n = 211) Pntr	HSD (n = 211) Blnt	HSD (n = 211) Unk	STD (n = 211) Pntr	STD (n = 211) Blnt	STD (n = 211) Unk	Total (n = 422) Pntr	Total (n = 422) Blnt	Total (n = 422) Unk
Houston	84	16	1	95	8	0	179	24	1
Denver	37	26	3	32	30	2	69	56	5
Milwaukee	32	12	0	24	19	1	56	31	1
Total	153	54	4	151	57	3	304	111	7

HSD, hypertonic saline/dextran treatment group; STD, standard treatment group; Pntr, penetrating injury, Blnt, blunt injury; Unk, unknown.

TABLE 3. *Injury Scores and Survival Between Groups*

	HSD	STD
Injury Scores and Survival	M ± SD	M ± SD
Revised trauma score		
Pretreatment	5.97 ± 1.60	5.93 ± 1.75
Emergency center	7.43 ± 0.97	7.25 ± 1.75
Injury severity score	19 ± 13	19 ± 15
TRISS (probability of survival)	0.84 ± 0.29	0.83 ± 0.32
24-hour survival (overall)	88%	82%
Penetrating injury	89%	82%
Blunt injury	84%	82%

HSD, hypertonic saline/dextran treatment group; STD, standard treatment group; M, mean; SD, standard deviation.

survival estimated using the TRISS method was identical to the observed 24-hour survival (Table 3). No statistically significant difference was demonstrated among the demographic data between treatment groups (Table 1) (p = 0.806).

Ambulance Times

The mean ambulance times from dispatch to arrival at the scene, at the scene, and during transport to the hospital were 7, 12.5, and 10 minutes, respectively, with no differences between treatment groups. The Houston ambulance dispatch times were slightly longer, Milwaukee ambulance scene times were slightly longer, and Denver ambulance transport times were shorter. The average 29- to 30-minute prehospital time from dispatch to arrival at the trauma center was similar to that in previous studies from urban centers.

Survival

There were 77 deaths. Sixty-five of the 77 deaths (84%) occurred within the first 24 hours, and only three deaths occurred after 7 days. There was an apparent but not significantly different trend for a better survival among the hypertonic saline/dextran group (Fig. 1). Of the 77 deaths, 35 occurred in patients given hypertonic saline/dextran (83% survival) and 42 patients given standard solution (80% survival). There was little difference in survival outcome in those patients with blunt injuries (79%) and those with penetrating injuries (83%). This finding was true for etiology comparisons as well. Survival was calculated for those patients requiring surgery, presuming these patients were more significantly injured. In this group there was a significant treatment effect in favor of hypertonic saline/dextran ($p = 0.02$). This effect was significant in those patients sustaining penetrating trauma ($p = 0.01$), but not in those with blunt trauma. In the center with the highest enrollment of patients with penetrating injuries, the survival was 88% in patients given hypertonic saline *versus* 77% in those receiving Ringer's lactate ($p = 0.06$). Using the Cox proportional hazards model with time to death or loss to follow-up and logistic regression with 24-hour survival indicated that the important predictors of survival were Injury Severity Score, preinfusion Trauma Score, and patient age. Introduction of these covariables into the analysis did not help differentiate between survival in the treatment groups.

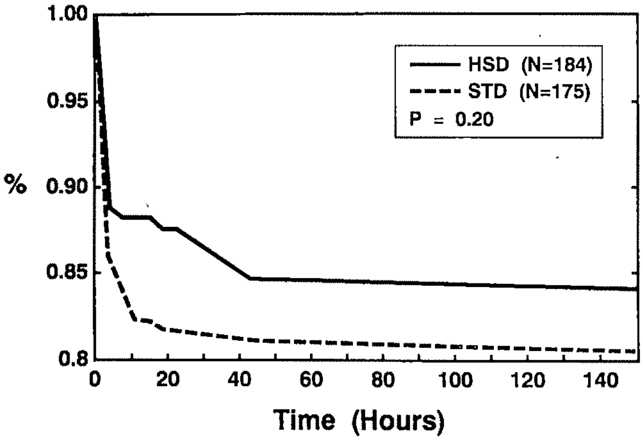

FIG. 1. Life table survival analysis for efficacy patients comparing patients receiving hypertonic saline/dextran (HSD) and standard (STD) treatments.

It proved to be impractical, in most cases, to follow the patients once they had been discharged or transferred from the trauma centers. Many gave fictitious names, addresses, and telephone numbers. Only 22 patients were followed for as long as 30 days. Consequently any comparison of 30-day survival rates, a secondary end point for the study, was not performed.

Change in Revised Trauma Score

Changes in the Revised Trauma Score between preinfusion and the emergency center were analyzed by treat-

TABLE 4. *Physiologic Data-Elements of the Revised Trauma Score*

	HSD	STD	
Physiologic Parameters	Mean ± SD	Mean ± SD	p Value
Systolic blood pressure-pre	74 ± 12	75 ± 16	NS
Systolic blood pressure-EC	121 ± 28	111 ± 27	0.024
Resp-pre	20 ± 7	20 ± 6	NS
Resp-EC	21 ± 6	21 ± 5	NS
GCS-pre	12.6 ± 3.8	12.3 ± 3.9	NS
GCS-EC	13.0 ± 3.8	12.6 ± 4.0	NS
Revised trauma score-pre	5.97 ± 1.61	5.93 ± 1.75	
Revised trauma score-EC	7.43 ± 0.97	7.25 ± 1.16*	

* Although not significant between treatment groups, the revised trauma score was significant ($p < 0.001$) over time between pretreatment and arrival at the emergency center.

HSD, hypertonic saline/dextran treatment group; STD, standard treatment group; Resp, respiratory rate (breaths/minute); GCS, Glascow trauma score; pre, prehospital treatment; EC, emergency center; NS, not significant.

ment using analysis of variance (Table 1). There was a statistical difference in the revised trauma score between pretreatment baseline and in the emergency centers in both the treatment and control groups ($p < 0.01$). No statistically significant differences between treatment groups were apparent. In an analysis of the components of the revised trauma score, the pulse rate was significantly different over time (preinfusion *versus* 30 minutes/24 hours, analysis of variance, $p < 0.01$), but not between injury type or treatment groups. Systemic blood pressure significantly increased over time, and exhibited a more rapid initial rise in patients receiving the hypertonic saline dextran (Table 4, Fig. 2). Respiratory rates were affected over time, but not between treatment groups. The mean Glasgow coma score (12.6) was not significantly different over time nor by treatment group (Table 5).

TABLE 5. *Summary of Postadmission Complications (Number of Occurrences, Not Patients)*

Complication	HSD	STD	Total
Specified in protocol			
Coagulopathy	2	8	10
Pneumonia	3	5	8
Sepsis	0	3	3
Abdominal abscess	1	1	2
Pulmonary embolism	0	2	2
ARDS	0	2	2
Acute renal failure	0	1	1
Heart failure	0	1	1
Dead bowel	0	1	1
Others			
Cardiac arrest	1	0	1
Total	7 (in 7 patients)	24 (77%) (in 13 patients)	31

HSD, hypertonic saline/dextran treatment group; STD, standard treatment group; ARDS, adult respiratory distress syndrome.

Complications

Twenty patients had a total of 31 postadmission complications, 24 of which occurred in 13 patients receiving standard treatment (Table 5) and seven who received hypertonic solutions. Seven of these patients subsequently died, only one of which had received hypertonic solution. Ten patients had coagulopathies, only two of whom received hypertonic saline/dextran. No problems were observed with blood cross-matching, central pontine myelitis, or seizures. All of these complications were considered by the investigators to be secondary to the injuries.

Fluid and Urine Output

Although the mean volume of fluids administered was not different among groups in the centers, a consistently lower mean volume of administered fluid was required in the patients receiving hypertonic saline/dextran prehospital, in the emergency center, in the operating room, and in the composite initial 24-hour totals (Table 6). The mean urinary outputs in the emergency center, operating room, and composite 24-hour totals were similar for all study groups.

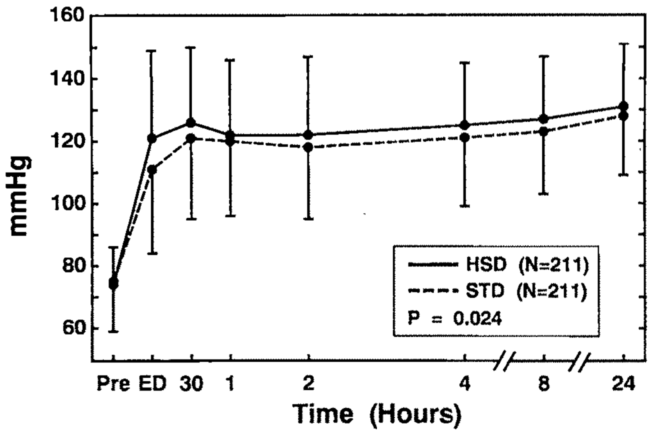

FIG. 2. Graft comparing the mean systemic blood pressures (and standard deviations, SD) between treatment groups.

TABLE 6. *Summary of Fluid Balance (ml of fluid)*

Fluid Balance	HSD	STD
Fluid intake		
Prehospital	1087 ± 671	1171 ± 771
Emergency center	1902 ± 1340	2543 ± 2075
Operating room	7639 ± 7719	8830 ± 7652
24-hour totals	9183 ± 8487	10707 ± 8896
Urine output		
Emergency center	574 ± 617	419 ± 680
Operating room	1277 ± 1216	1221 ± 1114
24-hour totals	3310 ± 2076	3337 ± 2293

HSD, hypertonic saline/dextran treatment group; STD, standard treatment group.

Laboratory Data

Extensive laboratory analysis was performed in the emergency center, at 2 or 4 hours and 24 hours after admission. The only significant differences between the treatment groups were the hematocrit in the emergency center, potassium at 4 hours, chloride and sodium in the emergency center, and at 2, 4, and 24 hours after admission, and osmolality in the emergency center, at 2 and 4 hours after admission (Table 6). The blood alcohol levels between groups were identical. Of note, the serum osmolalities were identical between treatment groups at 291 and 293 mOsm, respectively, at the 24-hour determination. Serum sodium levels were significantly higher in the hypertonic saline/dextran group as compared with standard therapy group at all times measured (at the emergency center, 2, 4, and 24 hours after admission) (Fig. 3). Twenty patients had serum sodium levels exceeding 155 mEq/L, all but one in the hypertonic saline/dextran group. Six of these 20 patients died; one was in the standard

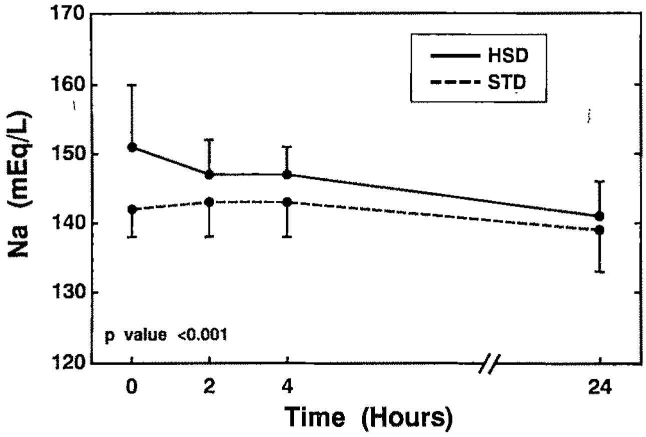

FIG. 3. Graft comparing the mean serum sodium levels (and standard deviations) between treatment groups.

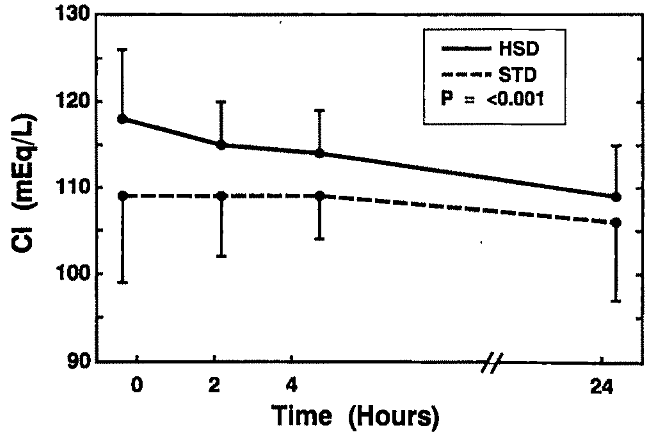

FIG. 4. Graft comparing the mean serum chloride levels (and standard deviations) between treatment groups.

treatment group (Table 7). The deaths were due to the injury, not to the hypernatremia. There were no neurologic symptoms of seizures, somnolence, or coma, or other adverse clinical symptoms of hypernatremia. The mean serum chloride level was significantly elevated in the hypertonic saline/dextran group at all times through 24 hours after injury (Fig. 4). This difference was most obvious at the determinations made in the emergency center. The serum potassium and creatinine levels were identical for both study groups (Table 8). Serum potassium levels in both groups remained normal through the first 24 hours of hospitalization. Although the serum bicarbonate levels were identical for both study groups in the emergency center and through 24 hours of measurement, a lower bicarbonate level was noted among the patients from Denver, because of the higher altitude (Table 9). All aspects of the blood gases through 24 hours demonstrated no statistically significant difference between treatment groups (Table 8). The only appreciable difference was seen in the Denver cohort of patients, where the partial pressure of carbon dioxide (P_{CO_2}) averaged 6 mmHg lower than the other two centers. Again, this difference was attributed to the higher altitude of Denver. Prothrombin times, partial thromboplastin time, and platelet counts were assessed as a gross evaluation of clotting studies. Although 10 patients exhibited clinical signs of a coagulopathy (and these patients had altered clotting studies), no significant difference between the study groups in these three coagulation parameters was noted. The mean white blood counts were identical for both groups. The mean hematocrit levels in the emergency center were lower in the hypertonic saline/dextran cohort (32%) than in the standard treatment group (34%). Hematocrit levels were not different between groups at subsequent determinations.

TABLE 7. *Patients with Serum Sodium Levels Greater than 155 mEq/L Who Died*

Treatment	Emergency Center Sodium (mEq/L)	Survival (hours)	Injury
HSD	156	26.1	SW to left ventricle
HSD	164	0.9	Air embolism
HSD	169	2.3	GSW to IVC & iliac artery
HSD	169	6.8	Massive head injury
HSD	237	7.0	SW right ventricle & coronary artery
STD	163	317.6	SW right ventricle

HSD, hypertonic saline/dextran treatment group; STD, standard treatment group; SW, stab wound; GSW, gunshot wound; IVC, inferior vena cava.

Safety Analysis

Deaths, postadmission complications, and any specific acute reactions were analyzed to assure safety of the treatments or study solutions. Deaths and complications in all patients were considered the result of initial injury or known complications of the injury. The complication and

TABLE 8. *Laboratory Values in the Emergency Center*

	HSD	STD	
Laboratory Values	Mean ± SD	Mean ± SD	p Value
Sodium (mEq/L)	151 ± 9	142 ± 4	<0.001
Chloride (mEq/L)	118 ± 8	109 ± 10	<0.001
Potassium (mEq/L)	3.8 ± 0.6	3.9 ± 0.7	NS
Bicarbonate (mEq/L)	19.6 ± 4.3	19.2 ± 5.0	NS
Osmolality (mOsm)	343 ± 34	328 ± 41	<0.001
Creatinine (mg/dL)	1.1 ± 0.3	1.1 ± 0.3	NS
Hematocrit (%)	32 ± 7	34 ± 8	0.001
Prothrombin time	12.7 ± 2.4	12.5 ± 2.1	NS
Partial thromboplastin time	33 ± 24	32 ± 17	NS
pH	7.29 ± 0.11	7.30 ± 0.14	NS
pO2 (mmHg)	179 ± 136	176 ± 131	NS
pCO2 (mmHg)	37 ± 10	36 ± 10	NS
Blood alcohol (%)	0.135 ± 0.11	0.139 ± 0.11	NS

HSD, hypertonic saline/dextran treatment group; STD, standard treatment group; NS, nonsignificant; SD, standard deviation.

TABLE 9. *Summary of Serum Bicarbonate Levels (mEq/L)*

Time in Hospital	Ben Taub General Hospital	Denver General Hospital	Milwaukee County Medical Complex	Total
Emergency center				
HSD	21.6 5.0	16.9 3.8	19.1 3.7	19.6 4.3
STD	20.4 5.8	16.7 4.4	19.9 3.9	19.2 5.0
2 hours				
HSD	21.6 4.5	17.2 3.6	20.8 2.5	20.0 3.8
STD	22.2 4.7	16.9 3.9	22.1 4.4	21.1 4.5
4 hours				
HSD	23.0 3.2	17.8 3.4	22.4 2.9	20.8 3.2
STD	24.1 4.5	18.2 3.1	21.3 3.8	21.7 3.9
24 hours				
HSD	26.0 4.1	22.5 3.4	24.2 2.5	24.5 3.6
STD	29.7 3.7	22.3 3.4	23.6 2.2	24.2 3.4

HSD, hypertonic saline/dextran treatment group; STD, standard treatment group.

death rates were not different between treatment groups. No cases of dextran-induced anaphylactoid reactions or seizures were reported.

Discussion

In this first United States multicenter study of hypertonic saline, the infusion of 7.5% NaCL in 6% dextran 70 in hypotensive patients was not shown to improve 24-hour survival. This lack of efficacy probably was due to experimental design. After the initial infusion of 250 mL of study solution, patients continued to receive resuscitative fluid at the discretion of the treating physicians. Therefore the use of additional fluids as necessary to achieve normotension was expected to decrease the observed differences in survival between treatment groups, as both groups were maximally resuscitated. Both control and treatment patients received similar volumes of resuscitative fluids. There was not a comparison of a small volume of hypertonic solution with a routine volume of a balanced crystalloid solution, nor was there a comparison of a small volume of hypertonic solution to no preoperative fluid resuscitation at all. Thus a small volume (250 mL) of hypertonic solution merely has an additive effect on routine resuscitation. Although within the limits of the experimental design the hypertonic saline/dextran cohort did not display superiority in efficacy, neither did this group show an inferiority in either the primary or secondary end points.

Restoration of lost intravascular fluid volume has been the objective of the resuscitation of the patient with post-traumatic hypotension for the major portion of this century. This logic has been based on considerable laboratory and clinical work.[1-12,19,59,60] The increase in fluid volume as well as the accompanying increase in blood pressure, tissue perfusion, and oxygen transport have been assumed to contribute to an increased opportunity for both operative and nonoperative treatment strategies in the hospital. With the advent of Emergency Medical Services, even in rural areas, and an ever-present threat of global warfare with its presumed longer transport and supply times, a smaller volume, equally effective or even of superior resuscitative effectiveness, would be desirable.[19-21,23,24,31,42,43,45,61-71] Hypertonic saline solutions, with and without the addition of dextran, seem to satisfy that logic and have been extensively studied in the laboratory and a frequent suggestion that solutions containing dextran have a distinct advantage in resuscitation from shock.[17,18,21,25-27,29,30,35-40,72-75] Many of the experimental animal studies use a modified Wigger's preparation of 'controlled' hemorrhage. The beneficial hemodymamic effects of hypertonic solutions are increased systemic blood pressure, increased cardiac output, improved oxygen transport, and increased mesenteric and coronary blood flow.[11,17,18,29,40,76,77] Through increasing microcirculation and recruitment of extravascular water, hypertonic solutions have been shown to cause vasodilation, increased myocardial contractility, and redistribution of extracellular and interstitial fluid.[19,21,25-28,35,77]

Evaluations of hypertonic solutions in patients with burns,[78-81] cerebral injury,[68,82-88] and nontraumatic hemorrhage[17,31,61,69,71] also have been reported. These studies have bearing on the general subject of the physiologic effects of hypertonic solutions and indirectly relate to traumatic hypotension, but are, in general, beyond the scope of this directed multicenter study. To test the efficacy hypothesis on post-traumatic hypotension, a real-time, real-patient clinical trail in the prehospital environment is required.

This and other similar clinical studies have used a maximum of 250 mL and a maximum of 7.5% NaCl solutions. A theoretical disadvantage exists in using larger volumes of this concentration, because complications of hypernatremia might ensue. Furthermore, there is a maximum recruitment of intracellular and interstitial fluid that would be tolerated. In the logistics of the field environment, especially if uncontrolled, hypertonic saline solutions would not be as 'forgiving' as isotonic solutions.

In the post-traumatic hypotensive patient, Holcroft et al.[20,43,44,64] have shown a beneficial effect of hypertonic solutions on physiologic parameters, especially blood pressure, but not survival.[44] This group has also reported on the safety of a limited volume of hypertonic saline (250 mL). This study also demonstrates the safety of a limited volume of prehospital administration of a 7.5% NaCl in 6% dextran 70. Of the 211 patients who were infused with the hypertonic saline/dextran solution, none of the complications or adverse reactions were attributable to the treatment solution. This experience is in keeping with the lack of adverse events noted in innumerable animal experiments in which a small bolus of the hypertonic saline/dextran solutions was infused.

Based on an analysis of previous reports from Sacramento and a pilot study in Houston, it was originally projected that a minimum of 700 patients would be required to determine a significant efficacy difference between the study solutions. Because of an unanticipated lower than expected mean ISS, it was determined that more than 1200 patients would be needed to detect a significant difference, and this multicentered study was terminated prematurely at the second interim analysis. Furthermore this study was performed in cities with relative rapid transport, rapid emergency center care, and rapid transport to the operating room, and may not be a realistic evaluation for rural trauma patients or the military environment.

In at least two laboratories using models of 'uncontrolled' shock, resuscitation before control of the hemorrhage has caused investigators to question the use of mechanisms to raise the blood pressure.[3,33,89–91] The concept of maintaining a lower than normal blood pressure in the post-traumatic hypotensive patient has even been raised in the clinical setting.[1–3,8–10,13,46,91]

In conclusion this and other recent clinical studies have shown that the infusion of 250 mL of 7.5% NaCl in 6% dextran is as effective as standard resuscitation solutions in the prehospital management of traumatic hypotension. Within the experimental design, this solution may also offer a potential benefit in a subgroup of patients with penetrating injury and active hemorrhage and requiring urgent laparotomy or thoracotomy. Because the solution as given appears safe, a more rigid evaluation of 250 mL of 7.5% NaCl solutions, with and without dextran, and compared with larger/routine volumes of traditional resuscitation fluids, is justifiable.

Acknowledgments

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Management of Penetrating Colon Injuries

A Prospective Randomized Trial

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Fifty-six patients with penetrating colon injuries were entered into a randomized prospective study. Management of the colon injury was not dependent on the number of associated injuries, amount of fecal contamination, shock, or blood requirements. Twenty-eight patients were treated with primary repair or resection and anastomosis and 28 patients were treated by diversion (24 colostomy, 3 ileostomy, 1 jejunostomy). The average Penetrating Abdominal Trauma Index score was 23.9 for the diversion group and 26 for the primary repair group. There were five (17.9%) septic-related complications in the diversion group. This included four intra-abdominal abscesses and one subcutaneous wound infection. There were six (21.4%) septic-related complications in the primary repair group. This included one wound infection, two positive blood cultures, and three intra-abdominal abscesses. There were no episodes of suture line failure in the primary repair/anastomosis group. The authors conclude that, independent of associated risk factors, primary repair or resection and anastomosis should be considered for treatment of all patients in the civilian population with penetrating colon wounds.

THE MANAGEMENT OF the colon injury remains controversial in spite of a number of divergent reports during the past decade. Argument continues over the propriety of ostomy to divert such injuries *versus* primary repair without stoma.

Most recent retrospective investigations favor an aggressive approach with primary repair.[1-3] Only one prospective, randomized study analyzing diversion *versus* primary repair has been published, however.[4] That study showed an advantage to primary repair in selected cases. The study was flawed, however, by inclusion of criteria for obligatory diversion before randomization, thereby eliminating 48% of patients from the study.

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Civilian injuries resulting in colonic perforation continue to represent a significant problem in the United States, particularly in the urban sector. With the psychological, financial, and physical drawbacks of an ostomy and subsequent takedown, the question of the superiority of diversion over primary repair of colon injury is worthy of further research.

With this in mind, we initiated a prospective, randomized study, without exclusion of any patients, evaluating the treatment of intraperitoneal large bowel injury by diversion *versus* primary repair. Patients with extraperitoneal rectal injuries in association with intraperitoneal injuries were excluded. This report describes the results in the first 56 patients.

Materials and Methods

Between August 1987 and June 1990, all patients with a potential penetrating intraperitoneal large bowel injury admitted to the Louisiana State University trauma service at Charity Hospital at New Orleans were considered eligible for entry into the study. Standard resuscitative measures were performed on all patients according to Advanced Trauma Life Support (ATLS) protocol. Nasogastric and urinary catheters were placed. Depending on the response to resuscitation, patients were evaluated with indicated radiographic and endoscopic tests in selected cases. All patients received perioperative broad-spectrum systemic antibiotics. At the time of laparotomy, those patients found to have one or more penetrating colon injuries were randomized to either 'diversion' or 'primary repair.'

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Randomization was accomplished with a table of random two numbers. Diversion was defined as (1) exteriorization of the injury; (2) resection of the injury with exteriorization of the proximal segment and either exteriorization or closure of the distal line of resection; or (3) debridement, if indicated, and simple closure of perforations with formation of a loop or end stoma proximal to the injury. Primary repair was defined as (1) debridement, if indicated, with simple closure of the perforations or (2) resection of a segment of large bowel containing perforations followed by anastomosis. All perforations were closed using accepted suture or staple methods. Patients with multiple colon injuries were included in the study. The peritoneal cavity in all patients was irrigated with sterile saline solution before fascial closure. Skin wounds were left open to heal by secondary intention or by delayed primary closure at approximately 5 days after operation. Administration of systemic antibiotics beyond 48 hours was permitted only when other extra-abdominal injuries dictated, for example, open fracture. Patient care was by surgical residents with close supervision by attending staff throughout the hospital course. Patient data were collected with the emphasis on success or failure of the method of management of the colon injury and the subsequent effect on the patient's clinical course. Similar data were retrieved for those patients treated with diversion who later underwent stoma closure.

Results

Of the 56 patients, 28 were randomized into each group. Data were collected concurrently and complications and outcome recorded.

The majority of patients in each group were young men. The average age for the primary repair group was 26 years (range, 17 to 58 years); and for the diversion group, 23 years (range, 14 to 61 years). There were 27 men and 1 woman in the primary repair group and 25 men and 3 women in the diversion group. All patients were from the New Orleans area and were brought to the Charity Hospital accident room shortly after sustaining injury. Average time from arrival at the Accident Room to operation was 116 minutes for primary repair *versus* 91 minutes for the diversion group. There was a single patient in the primary repair group whose stab wound to the abdomen was treated nonoperatively at first. This patient's time to operation was 705 minutes. Both groups had a preponderance of gunshot wounds as the cause of penetrating injury (Table 1). In the diversion group, there was one patient with a shotgun wound.

TABLE 1. *Mechanism of Injury*

Mechanism	Primary Repair	Diversion
Gunshot wound	24	27
Stab	4	0
Shotgun	0	1

TABLE 2. *Transfusions*

Number Units PRBC	Primary Repair	Diversion
0	15	17
1–4	8	3
>4	5	8

PRBC, packed red blood cells.

At the time of arrival in the accident room, the majority of patients were hemodynamically stable. Shock, defined by a systolic blood pressure less than 80 mmHg, was present in three patients in the diversion group and one patient in the primary repair group. No blood transfusions were required in 32 patients. Packed red blood cell (PRBC) administration to others is shown in Table 2. More than 4 units of PRBC were required in eight patients in the diversion group and five patients in the primary repair group.

All patients were explored through midline incisions. Colon wounds and associated injuries were evaluated and graded according to the Penetrating Abdominal Trauma Index (PATI).[5] All associated abdominal organs injured were evaluated and treated accordingly. The small bowel was the other organ injured most commonly (Table 3). The number of injuries, including colon injury, was similar in both groups (Table 4). The average PATI score for the primary repair group was 26, with a range of 8 to 77, and for the diversion group the score was 23.9, with a range of 12 to 55.

There was no difference between the two groups with respect to the grade of colon injury according to the colon

TABLE 3. *Associated Intra-abdominal Injuries*

Organs	Primary Repair	Diversion
Small bowel	15	21
Duodenum	7	4
Stomach	6	4
Liver	6	4
Major vascular	5	4
Kidney	4	3
Pancreas	2	2
Ureter	1	3
Diaphragm	2	—
Gallbladder	1	—
Spleen	1	—

TABLE 4. *Total Number Organs Injured*

Number	Primary Repair	Diversion
1	3	2
2–3	19	19
>4	6	7

injury severity scale (Table 5) or location of injury (Fig 1). There was a single colon injury in 25 patients in the primary repair group and in 20 patients in the diversion group. Multiple colon injuries were found in 11 patients (Table 6). Of particular note is the presence of a similar number of left-sided injuries in each treatment group. The majority of injuries were grades III and IV. There were no grade I colon injuries in either group.

Of the 28 patients in the diversion group, 21 were diverted by a colostomy (12 end and 9 loop) and 6 by ileostomy (3 end and 3 loop). One patient had a shotgun wound requiring resection of a large portion of small bowel and colon and underwent an end jejunostomy.

Of the patients in the primary repair group, 11 underwent resection with anastomosis, (10 stapled functional end to end, 1 sutured) and 17 underwent debridement and closure (5 stapled, 12 sutured). There were no anastomotic leaks in the primary repair group.

Complications developed with equal frequency in both groups (Table 7). Eighteen patients in the diversion group and 19 patients in the primary repair group had no complications and an uneventful recovery and discharge. In the diversion group, there was one patient who developed a soft tissue infection in the anterior abdominal wall. This patient had a shotgun wound and developed a subcutaneous abscess between the incision and stoma. In the primary repair group, there was one wound infection that occurred after the wound was closed by delayed primary closure. There were two fistulas (one pancreatic and one duodenal) in the diversion group. Both healed by nonoperative treatment with total parenteral nutrition.

Patients who developed intra-abdominal abscesses were evaluated for known risk factors (Table 8). The length of time from arrival in the accident room to operation was not different from the overall group for the seven patients who developed intra-abdominal abscesses. One patient was 61 years old (older than average), but the remaining six patients were all between the ages of 17 and 33. Penetrating Abdominal Trauma Index score was less than 25 in four patients and more than 25 in three. Blood transfusion was required in six of the seven patients, but shock was only present in one of the seven patients. There was no difference in the incidence of abscess between the diversion and primary repair groups. Two of the three patients with intra-abdominal abscess in the primary repair group had resection and anastomosis. The number of associated injuries, number of colon injuries, and grade of the worst colon injury were similar.

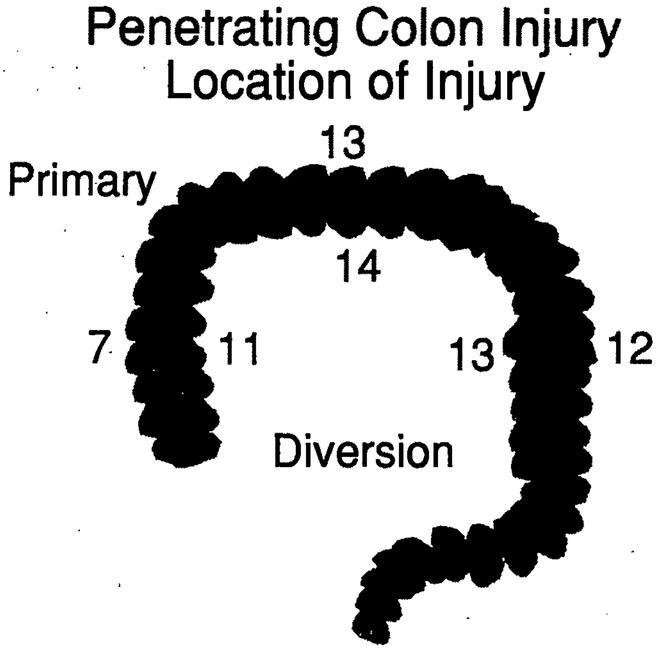

FIG. 1. Location of injuries, primary repair *versus* diversion.

All dehiscences occurred in the diversion group (Table 9). One patient was 61 years old, received 10 units of PRBCs, and developed an intra-abdominal abscess. In the other two patients, no contributing factors could be identified that predisposed the patient to dehiscence.

Drains were used as indicated for associated injuries; no colon repair was drained.

To date stoma closure has been performed on 22 pa-

TABLE 5. *Colon Injury Severity Scale*

Worst Grade Injury	Primary Repair	Diversion
I	0	0
II	4	3
III	13	17
IV	7	5
V	4	3

TABLE 6. *Number Colon Injuries*

Number	Primary Repair	Diversion
1	25	20
2	2	6
3	1	2

TABLE 7. *Complications*

Complication	Primary Repair	Diversion
Intra-abdominal abscess	3	4
Dehiscence	0	3
Repeat operation	2	3
Duodenal leak	0	1
Pancreatic fistula	0	1
Ureteral stenosis	0	1
Wound infection	1	1
IVC thrombosis	1	0
BC+—no source	2	0
Respiratory failure	0	1
Phlebitis	0	1
Catheter sepsis	0	1
Atelectasis	1	1

IVC, inferior vena cava; BC+, blood culture positive without identifiable source.

tients. One patient with a colostomy had a spinal cord transection with paralysis and there is no plan for closure. Of the 22 patients closed, the average length of stay was 7.4 days (range, 4 to 11 days) for closure. The average interval from creation to closure of stoma was 120 days (range, 51 to 264 days). Twenty-one of twenty-two stomas were closed without complication. One patient with an ileostomy developed an enterocutaneous fistula after ileostomy closure. The fistula closed spontaneously after 18 days of hyperalimentation. Comparing length of stay for each group, including admission and readmission for colostomy closure, shows a longer stay for the diversion group than the primary repair group (18.8 days *versus* 12.8 days).

Discussion

Trends in the management of colonic injury in this century have been summarized by Nance.[6] Primary repair was favored early in the century until World War II, when Ogilvie's classic paper describing the British experience in the African desert and the mandate by the Surgeon General of the Armed Service Forces of the United States made colostomy proximal to or at the site of large bowel trauma the standard of care.[7,8] Woodhall and Ochsner[9] in 1951 suggested the safety of primary repair in selected patients with civilian colon injury. Diversion remained the standard of care during the period from 1950 to 1980, however. In the last 10 years, primary repair has assumed an increasing role in the treatment of colon injuries.[1-3]

TABLE 8. *Intra-abdominal Abscess*

Time to Surgery (min)	Age	PATI	Number Units PRBC	Shock
Diversion				
75	61	30	10	No
75	19	32	2	No
90	29	19	0	No
120	22	22	6	No
Primary repair				
105	33	24	4	Yes
58	32	77	8	No
58	31	18	2	No

PATI, Penetrating Abdominal Trauma Index; PRBC, packed red blood cells.

TABLE 9. *Wound Dehiscence: Diversion*

Time to Surgery (min)	Age	PATI	Number Units PRBC	Shock
24	30	22	0	No
35	22	20	0	No
75	61	30	10	No

PATI, Penetrating Abdominal Trauma Index; PRBC, packed red blood cells.

Stone and Fabian,[4] in a 1979 prospective randomized study of perforating colon injuries, clearly demonstrated that, in select patients, primary repair was effective when compared with colostomy. Moreover in some patients the colon-related morbidity rate of primary repair was less than that of diversion. As a 'randomized, prospective' study, this important paper was criticized on several points. A large number of patients (48%) were eliminated from randomization and assigned obligatory colostomy on the basis of parameters indicating severe injury (shock, excessive blood loss, more than two abdominal organs injured, excessive fecal contamination, delay in operation, colon injury requiring resection, major abdominal wall loss). In addition randomization was on the basis of the patient's hospital number, not the ideal method of blinding the surgeon obtaining consent of the patient.

Despite the criticisms of the report by Stone and Fabian, the importance of their investigation cannot be underestimated. The past decade has ushered in a number of

TABLE 10. *Comparison of Retrospective Studies*

Author		Wound Infection (%)	Intra-abdominal Abscesses (%)	Deaths (%)
Jurisich unpublished data	Colostomy	23	6	8.5
	Primary repair	9.4	3	2.6
George[3]	Colostomy	29	10	6.4
	Primary repair	8.6	5.5	1.4
Shannon[1]	Colostomy	12	25	2*
	Primary repair	7	14	1
Burch[2]	Colostomy	5.3	16.7	9.2
	Primary repair	4.5	5.3	1.6

* Septic-related death.

retrospective studies from major trauma centers on the treatment of the injured colon. These studies and those of our institution's retrospective data (unpublished) tend to agree with Stone and Fabian (Table 10). These retrospective data have shown that patients often can be treated successfully with primary repair even in the presence of the adverse conditions that mandated obligatory colostomy by Stone and Fabian.[4]

George and colleagues prospectively performed primary repair in 95 of 102 patients (93%) with colon injury.[10] The incidence of wound infection was 14.8% and intra-abdominal abscess/peritonitis was 13.6%. There was one suture line failure in the anastomosis group.

Many advances in prehospital care, resuscitation, blood banking, and critical care have changed the natural course of the patient with civilian colon injury as compared with 50 years ago. When victims of colon trauma die in the early postinjury period, death is usually due to other injuries, such as great vessel perforation or head injury. The usual problems associated with colon injury are infections with subsequent complications and, sometimes, death. The purported advantage of diversion over primary repair is the avoidance of a suture line leak as a potential source of intra-abdominal sepsis. In this study the incidence of colon-related complications did not differ between the two groups. The incidence of intra-abdominal abscess was 14% in the diversion group and 11% in the primary repair group. There was no suture line leak in the primary repair group.

It has been suggested that the PATI is a reliable basis for prediction of complications and a gauge for comparison of colon injury management. Moore and coworkers[5] found that when the PATI was 25 or less, the morbidity rates after stab wounds and gunshot wounds to the abdomen were 5% and 7%, respectively. A PATI of greater than 25 was associated with morbidity rates of 50% and 46%, respectively. Retrospectively, Nelken and Lewis[11] evaluated PATI, the Injury Severity Score (ISS), and the Flint Colon Injury Score. They concluded that PATI was superior to ISS and the Flint Score and recommended that the use of primary repair be expanded in civilian colon trauma. In our review the average PATI scores were 26 for the primary repair group and 23.9 in the diversion group. The number of patients with a PATI score greater than 25 or less than 25 was similar in each group (Table 11). For those patients in either group who developed colon-related complications, however, a PATI score greater than 25 was not an accurate predictor of complications in either group.

TABLE 11. *Comparison of PATI*

PATI	Primary Repair	Diversion
<25	18	20
>25	10	8

PATI, Penetrating Abdominal Trauma Index.

Exteriorized repair continues to be used in some centers as a method of management of colon trauma.[12] It requires a perforation, ideally on the antimesenteric border, amenable to suture closure rather than resection and capable of mobilization to the abdominal wall without excessive tension. Meticulous postoperative care is needed in the form of dressing changes. Despite enthusiastic proponents it never has been widely practiced. For these reasons we have not adopted the technique and did not think it appropriate for inclusion in this study.

The treatment of colon injury cannot be addressed satisfactorily without discussion of the psychological, financial, and physical consequences of colostomy and subsequent closure. Few would debate the psychological adjustments needed to adapt to life with a stoma, even if temporary. Similarly there is no doubt about the added expense of a second procedure for colostomy takedown, which involves not only the hospital and physician fees, but also the potential loss of work time during the hospitalization and recovery.

There is a wide variation in the recorded morbidity of stoma closure. Parks and Hastings[13] found a 36% complication rate and no deaths in a review of 83 patients subjected to colostomy closure at our institution after stoma formation for a variety of diagnoses, including injury. In contrast other reviews addressing colostomy closure after colon injury have found a much lower morbidity rate.[14-16] Crass et al.[15] studied 75 patients with colostomy takedown after colon injury and found a 5% overall complication rate, which correlates with the 5% morbidity rate in this study. Even though stoma closure after trauma can be done with a low morbidity rate, we agree with Jordan[17] that any operation, regardless of complication rate, is a potential cause of complications for the patient and that a colon injury should be managed with primary repair, avoiding colostomy and subsequent takedown, if it is judged safe to do so.

In addition to the morbidity rate of colostomy closure, the added time of hospitalization must be evaluated. Patients in this study who had colostomy closure had an average total length of hospital stay of 18.8 days *versus* 12.8 days for the primary repair group.

This review describes the results of a randomized prospective study of penetrating colon injury with no exclusion criteria. Evaluation of previously identified risk factors including PATI score greater than 25, number of transfusions, shock, and the time interval to operation was not beneficial in predicting increased morbidity rate from primary repair. The results suggest that virtually all patients with penetrating civilian colon trauma can be managed safely by primary repair.

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DISCUSSIONS

DR. ARTHUR C. BEALL, JR. (Houston, Texas): I rise to note that at this meeting in this hotel 20 years ago, I presented the Baylor experience on primary repair of colon injuries. I can well remember I was severely taken to task at that meeting by people who pointed out the experience in World War II, the Surgeon General's dictum regarding exteriorization, and so forth.

Obviously civilian colon injuries are different. They are usually stab wounds or low-velocity missiles as compared to high-velocity missiles in war time. The contamination is different. The time from injury to treatment is different. The follow-up is different. The treating surgeons are usually well-trained residents under supervision by experienced staff.

You cannot compare the two, but people have done that now for 40 years since Dr. Ochsner presented the Tulane experience on primary repair of colon injuries. People have quoted 'Those who cannot remember the past are condemned to repeat it.' However there are times that the past is different from the present. I hope we no longer have papers on primary repair of colon injuries in civilian practice introduced by saying there is still considerable controversy. I think it's time to lay that controversy to rest.

DR. TIMOTHY C. FABIAN (Memphis, Tennessee): I congratulate the authors on a very well-constructed prospective randomized study. It was very well controlled; the patients were well matched relative to location and grade of injury. Their data corroborate studies that I have been involved with in the past. And it certainly is convincing that primary repair is preferable to diversion for nondestructive colon wounds. I agree with Dr. Beall that there is little question that those wounds are appropriate. But I would still like to sound a word of caution about more injurious injuries that require resection and anastomosis. I think the jury is still out relative to those patients.

I would like to take a second and put some of this into perspective. In addition to Dr. Beall's work at Baylor 20 years ago, Woodall and Ochsner in New Orleans in 1951 were the first in the post-World War II period to suggest that civilian wounds were different and half of their patients could be repaired primarily. Regardless of that, it fell pretty much on deaf ears throughout the country, and most people began diverting most of these patients.

I would next like to refer to the study that Dr. Cohn mentioned, the perspective randomized study that was designed by Dr. Harlan Stone, and I was fortunate enough to participate in, presented at this meeting 12 years ago.

At that time primary repair was not a popular thing to do, as Dr. Beall suggested. Most people still were pretty skeptical that it could be done, safely, and at that time it was elected not to do it on everybody because there were no data available. Therefore certain patients were eliminated. Those who were in shock, who had more than two units of blood loss, significant delays in operation greater than 6 hours, multiple associated organ injuries, and excessive fecal contamination were not considered. If they had those, the patients underwent obligatory colostomy, which was 48% of the total population of 268 patients. The other 52% then were randomized to primary closure *versus* colostomy. As you can see, the intraperitoneal infection rate was significantly ($p = 0.05$) higher with colostomy. So that data demonstrated certainly that primary repair was not only as good but better for selected cases.

Two year ago we presented a study that was prospective but not comparative. It became fairly clear to us that the vast majority of colon injuries could be repaired primarily and did not require resection. At that time we had 83 patients with primary repair. We had 12 patients who had anastomoses. I would like to focus on the intra-abdominal sepsis rate, which was very similar to that data presented today. Our rate was 12% with primary repair. And, very importantly, there were no failures of repair in that study. Zero of 83.

Currently we are finding about a 1% failure rate with primary repair. However, with anastomosis, although there was a small number of patients, there was one failure. A patient leaked his anastomosis.

Subsequently we have had a fairly large series of colectomies with anastomosis and currently we're finding a 10% failure rate. It is clear to me that not all patients can be primarily anastomosed safely, and I think that is our next great challenge. Our risk factors have been major contamination and transfusions.

With that said, I would like to ask the following questions to the LSU group. First you noted that you only administer perioperative antibiotics for 48 hours. What is the rationale for using that limited amount of therapy in these patients, although that does satisfy my bias? I do not think there are any data available.

I would like to know about the 10% dehiscence rate in the resected patients. Was this due to necrotizing fascia or was this technical failure?

And finally are there any patients on whom you would not do a primary anastomosis today? I suspect that we will get a little more conservative as more data are available on that in the future.

DR. F. CARTER NANCE (Livingston, New Jersey): As a young man who came out of Saturday conferences with Dr. Cohn with a bloodied head by presenting patients who had primary colon wounds primarily closed, I would like to say better late than never, Dr. Cohn.

This is an important paper, and, as the previous discussants have indicated, settles the controversy and puts the burden of proof on the other side: that those who think that colostomy has a role in the management of colon injuries will have to come up with their own studies proving that it is better.

I would have preferred that this had been a larger study with more patients, but it is a pretty convincing one.

I also raise the issue of why we should separate military wounds from civilian wounds. We have well-trained surgeons out there in the desert now. This controversy started in the western desert, I will remind you, of Africa in 1944. And if one reads that paper the patients treated by primary suture did better than the patients with colostomy, despite the author's conclusion that mandatory colostomy should be performed.

Dr. DeBakey's own history of the Army's experience with the 19 patients who were treated by primary suture *versus* about 1500 patients treated by colostomy, those 19 patients did very well, despite the fact the surgeons were threatened with court martial if they did it.

In addition one of our distinguished former members, Dr. Ambrose Storch, recommended primary suture before the war when he wrote the manual on the treatment of abdominal injuries for the Army.

So I think that these studies all suggest that perhaps the military ought to also look into primary suture.

I have one question that is related to Dr. Fabian's comment. I noted that 40% of the patients in this group were treated by primary resection and anastomosis. That seems a bit high, and it seems to me that perhaps the authors were a little more aggressive about repair of the injuries. I would like to know whether they think their results would have been even better if they had made a more stringent attempt to close the wounds than to perform resection.

DR. DAVID FELICIANO (Rochester, New York): While the numbers are small in this series, the data are consistent with that previously reported by Stone, Fabian, Burch, and others, namely, that we all need to treat patients with traumatic perforations of the colon by ignoring much of what we learned about elective colon procedures in the past, *i.e.*, even without a bowel prep and even with feces in the operative field, at least a lateral repair of the colon is safe.

I have three short questions and comments for the authors. First please clarify your method of randomization, which was not clear in the manuscript.

Second, in John Burch's most recent series on colon injuries presented at the Western Surgical Association last month, 3 of 14 patients, or 21% of those with colocolostomies, developed anastomotic leaks. Two required reoperation, and one died. How many of your anastomoses were truly colocolostomies in this series rather than ileocolostomies?

And, again, do you really believe that your 11 stapled or sutured anastomoses that did not leak allow you to endorse enthusiastically this approach for all surgeons in trauma centers?

And I would like to repeat one of the other questions. Under what circumstances in 1991 would you no longer do a primary repair?

DR. CHARLES W. CHAPPUIS (Closing discussion): Dr. Fabian the rationale for 48 hours of antibiotics is based on this thinking: we do not think that there is any hard evidence in the literature today to support a longer course of antibiotics. And, in fact, there may be some reasonable evidence to support a lesser time period of antibiotics. But, nevertheless, we arbitrarily chose 48 hours as the period of time in which the perioperative antibiotics would be given.

With respect to the three patients who had a fascial dehiscence, they were all in the diversion group. One of the three had an intra-abdominal abscess. Two of the three were closed with a running suture. And I suspect that in light of any hard evidence to lay the blame on anything else, we would have to say that it was primarily technical errors that resulted in those fascial dehiscences.

Both Drs. Fabian and Feliciano asked when we would consider not doing a primary repair. Based on our study, the only patient in a civilian-type practice on whom we would give some strong consideration to not doing a primary repair would be that patient who has a spinal cord injury, because a colostomy may indeed facilitate this patient's care in the postoperative period.

Dr. Nance you asked if our results would have been better if we had closed more of these patients on whom we ended up doing resection and anastomosis. I am not sure the results would have been better. Of the 11 patients who had resection and anastomosis, the bulk were left colon injuries and most were grade 4 or 5 injuries, using the colon injury severity scale. Eight of the eleven were colocolostomies and there may have been some leniency used in doing a resection rather than a primary repair. Your point is well taken.

Dr. Feliciano asked about our randomization method. It was based on a table of two random numbers. Both surgeon and patient were blinded as to the method of repair or diversion until the time of exploration. And at that time a card was chosen. Once a card was chosen, no patients were subsequently eliminated from the study.

PRESIDENTIAL ADDRESS

A Surgical Perspective

MICHAEL E. DEBAKEY, M.D.

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MEDICAL PRACTICE, in one form or another, is rooted in the dawn of history and has paralleled, reflected, and sometimes influenced man's development. True cognizance and understanding of the societal role of surgery require a broad review of certain periods in the history of man's development. Neither necessary nor appropriate for this purpose, however, is a detailed historical account of surgery, which is available in many other publications.[1-22] Accordingly, historical considerations in this presentation are highly selective, with a focus on those personalities and events, including the social and cultural settings, pertinent to my thesis that surgeons, throughout recorded history, have viewed obstacles, adversaries, antiscientism, and anti-intellectualism as challenges and opportunities for improving their discipline by engaging in research, analysis of clinical experience, and other intellectual pursuits.

Recorded history began some 5000 years ago in two centers of civilization of nearly equal development situated in two of the world's great river systems: Mesopotamia, between the Euphrates and Tigris, and the Nile Valley of northeastern Africa.[23-33] Although recorded history was sparse in these early civilizations, medicine was already well developed, and its practitioners must have had a heritage of experience that was handed down by precept and word of mouth through earlier, perhaps countless, centuries.

Medical Papyri

Such a heritage is reflected in the Edwin Smith Egyptian papyrus (Fig. 1), believed by some historians to have been recorded between 1600 and 1500 B.C., and intended primarily for the use of a surgeon.[34] About the Smith papyrus, Ranke[35] wrote: "That the bulk of the main text goes back to the Old Kingdom [believed to have begun circa 3200 B.C.] is shown by a great number of glosses . . . added to the text of some of the cases, which explains words that in the course of time had become obsolete." Although Breasted[34] dated the Smith papyrus in the 17th century B.C., he believed it was a copy of a document at least 1000 years older. The significance of the Smith papyrus lies in the fact that surgery, as a well-defined discipline, assumed an important role in earliest recorded medical history. The Smith papyrus differs from other medical papyri in that it is the oldest in date of origin and the only one that deals primarily with surgery, describing a series of cases logically arranged, beginning at the head and progressing downward.

The other medical papyri consist essentially of a jumble of prayers, incantations, and fanciful prescriptions.[36] That surgery assumed high status at that time is further supported by the fact that the first treatise on surgery (dated about 2700 B.C.) was written by Imhotep, the Pharaoh's grand vizier (prime minister), whose status and reputation became so great that he was eventually declared to be a god and was worshiped for many years. Imhotep was the architect for the Step Pyramid Saqqara, the first massive monument of hewn stone, built in 2650 B.C. for King Zoser of Dynasty 3.[37] Called Ptah (Fig. 2), this god resembled in many ways the Greek god Asklepios of a much later period. Interestingly, while a few medical practitioners achieved sainthood, only a surgeon achieved godhood.

Early Egyptian Surgery

Reflected in these early writings was a high level of knowledge, with emphasis on correct diagnosis before initiation of treatment. These early Egyptian surgeons placed great value on hygiene and personal cleanliness, which undoubtedly contributed to the high quality of the surgery. The priests, who often functioned as physicians, empha-

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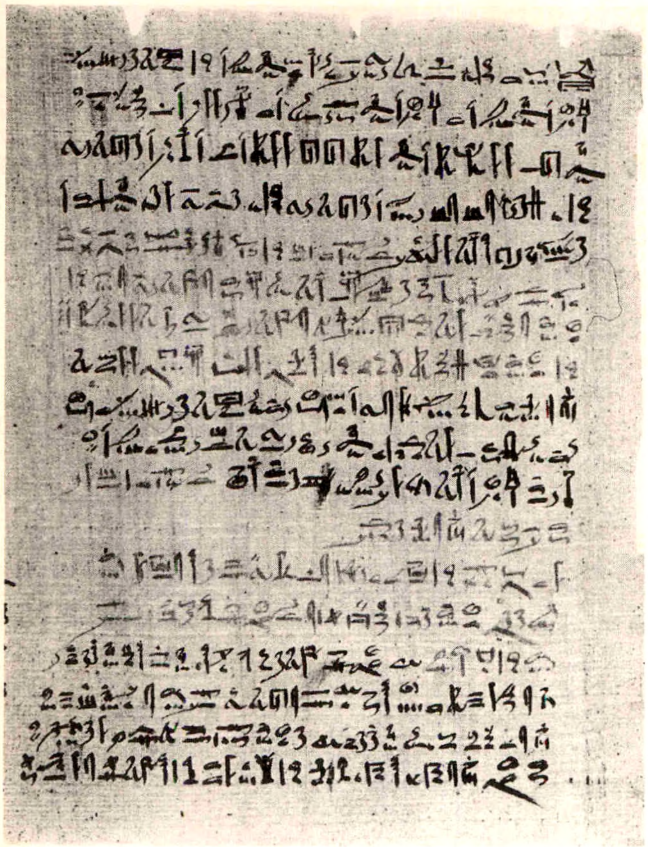

FIG. 1. Part of the Edwin Smith Papyrus considered to be the oldest surgical text in the world. (Courtesy of the National Library of Medicine, Bethesda, MD.)

sized ritual washings several times daily and, to avoid bringing dirt into the sanctuaries, had to be both head-shaven and circumcised (Fig. 3). Indeed, circumcision, depicted in a carving of the relief at Memphis (about 2200 B.C.), was one of the earliest surgical procedures. These early Egyptian surgeons were equipped with good surgical instruments made of flint, and later of bronze, with wooden handles, some of which may have been developed in connection with mummification (Fig. 4). There was also evidence of specialization, which sometimes extended to absurd lengths; in the courts of the Pharaohs, virtually every organ or illness had its own specialist. There was even a doctor who was ranked as "keeper of the royal anus." Some historians believe that such overdevelopment and specialization may have hastened a decline in the standards of medicine during the last 1000 years of the Egyptian empire.

Mesopotamian Surgery

In the other cradle of civilization, Mesopotamia, often called Babylonia, evidence of physicians also dates as early as 3000 B.C. Among the earliest surgeons was Urlugalidina (2300 B.C.), whose seal, displaying two knives together with Gods and plants of biology, can be seen today at the Louvre Museum of Paris. Of particular significance is the Code of Hammurabi (circa 2000 B.C.),[38] which recognized not only a regular medical profession but also the practice of some surgery. The Code provided strict regulations for the practice of medicine, which was government controlled, as reflected in these excerpts by Charles Edwards:

> If a doctor has treated a Freeman with a metal knife for a severe wound, and has cured the Freeman, or has opened a Freeman's tumor with a metal knife, and cured a Freeman's eye, then he shall receive ten shekels of silver.
>
> If a man's slave, the owner of the slave shall give two shekels of silver to the doctor.
>
> If a doctor has treated a man with a metal knife for a severe wound, and has caused the man to die . . . his hands shall be cut off.[39]

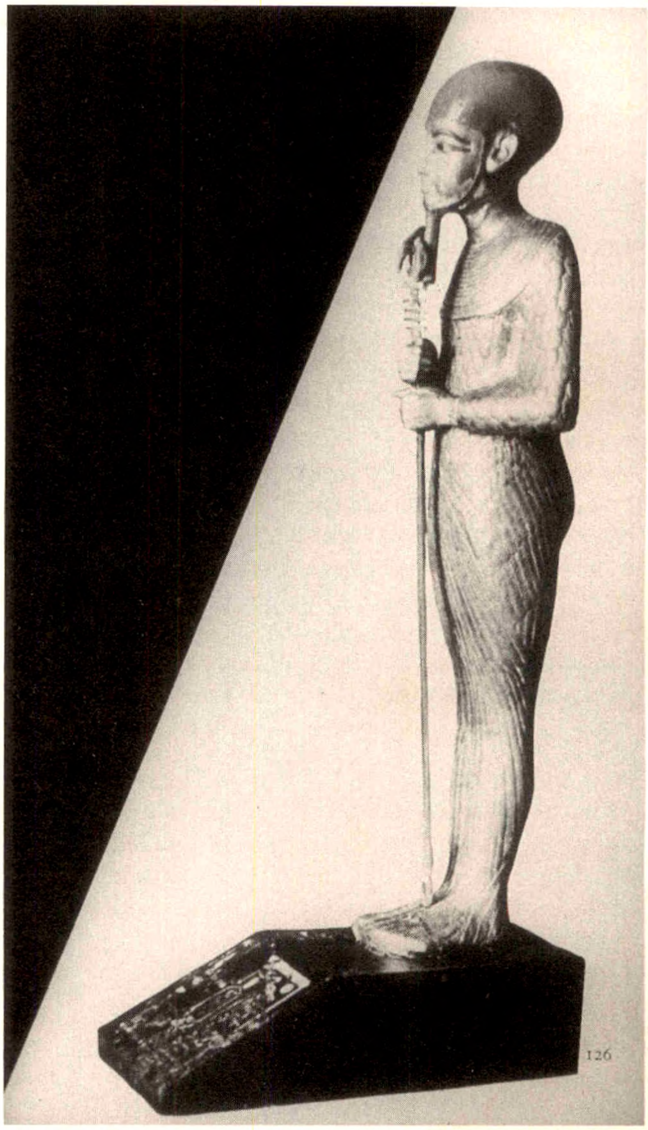

FIG. 2. Gold-painted wooden figure of Egyptian god, Ptah. (Courtesy of the Metropolitan Museum of Art, New York, NY.)

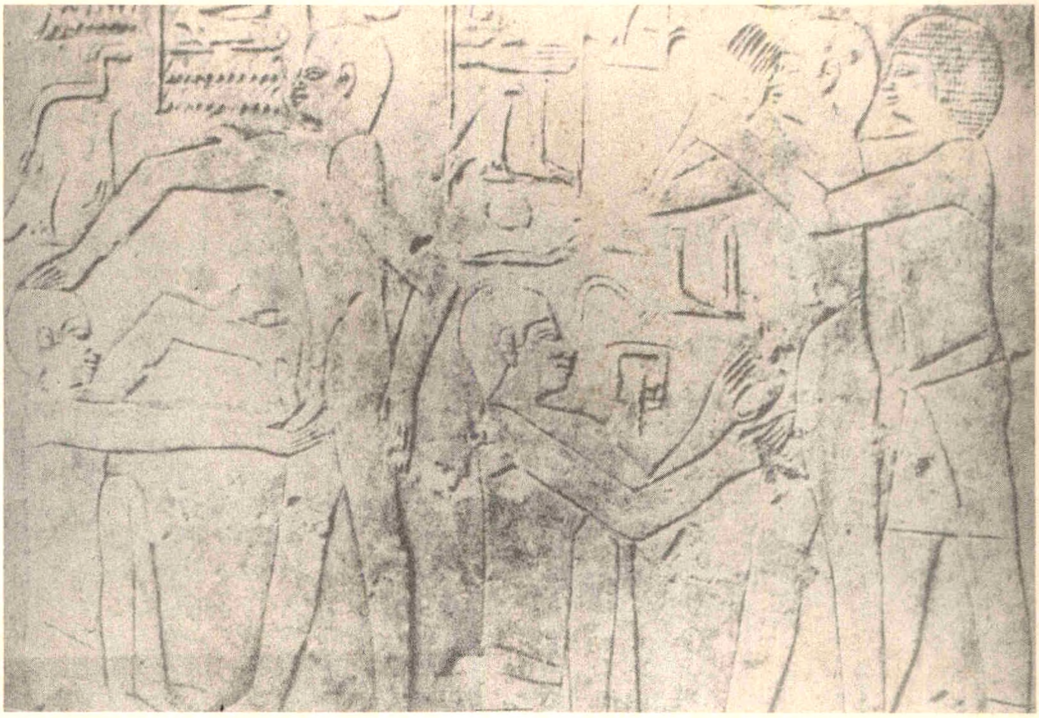

FIG. 3. Egyptian frieze of circumcision (circa 2200 B.C.). (Courtesy of AS Lyons and RJ Petrucelli,[22] Harry N. Abrams, Inc., New York, NY.)

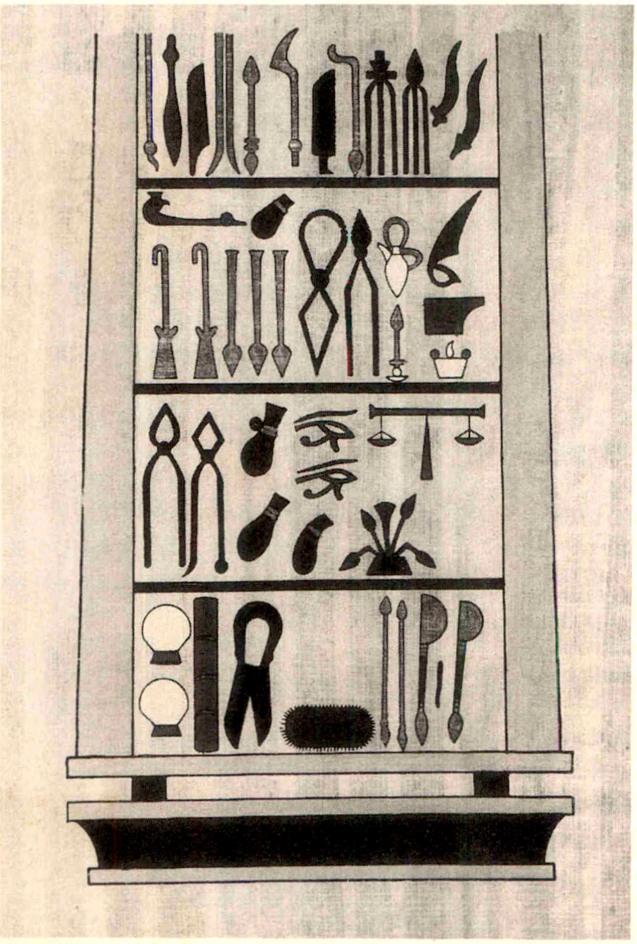

FIG. 4. Early Egyptian medical instruments.

Early Indian Surgery

Further evidence of the role of surgery in the early history of man appears in the Indian *Suśruta-samhitā* or "The Collection of Suśruta."[40,41] Although the exact dates of his lifetime are not known, most historians have placed him as early as 400 B.C. His philosophy has a somewhat modern perspective, as expressed in his *Samhitā:* "A physician, well versed in the principles of the science of medicine [Āyur Veda] but unskillful in his art through want of practice, loses his wit at the bedside of his patient, ... On the other hand, a physician, experienced in his art but deficient in knowledge . . . is condemned by all good men as a quack, and deserves capital punishment at the hands of the king. Both these classes of physicians are not to be trusted, because they are inexpert and half-educated. . . . A physician well versed in the principles of surgery, and experienced in the practice of medicine, is alone capable of curing distempers, just as only a two-wheeled cart can be of service in a field of battle." Such a statement gives lie early to the fallacious modern labeling of surgery by some as a noncognitive discipline.

Suśruta emphasized proper surgical instruments, having described some 125, including tongs, hooks, forceps, sharp scalpels, needles and thread, rectal speculum, and magnets for removal of foreign bodies. He described extensively various types of bandages and dressings, as well as surgical procedures, such as lithotomy, amputations, ophthalmic operations (especially for cataract), hemorrhoidectomy, alloplasty, operations for fistulae-in-ano, and rhinoplasty (Fig. 5).

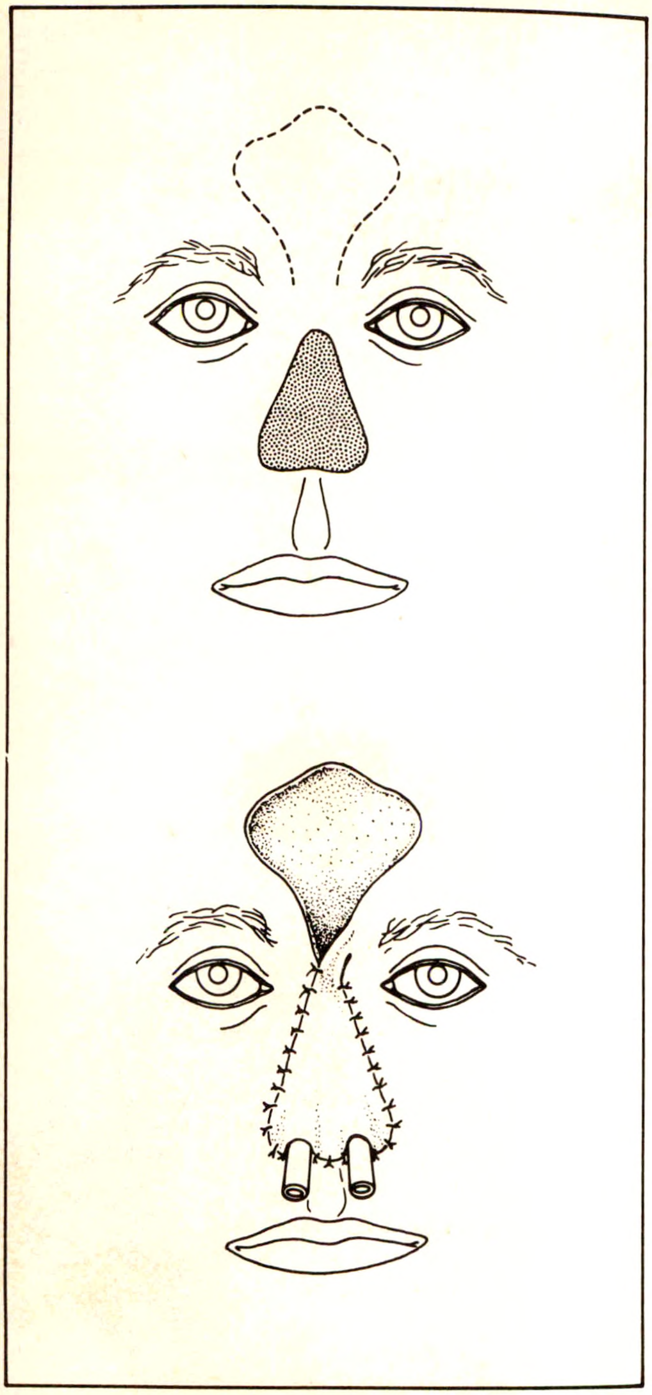

FIG. 5. Drawing from Suśruta showing method of nose restoration. (Courtesy of AS Lyons and RJ Petrucelli,[22] Harry N. Abrams, Inc., New York, NY.)

Greek Surgery

The rise of Western surgery had its origin in the peoples of Greece and Asia Minor. The Homeric poems, the *Iliad* and *Odyssey,* provide the oldest source of knowledge about Greek medicine.[42] Believed to have been composed around 700 B.C., these epics may be based on events and customs five or six centuries earlier. Asklepios was well established at this time as the god of medicine. According to Greek mythology, Asklepios was killed by Zeus after Hades, god of the underworld, became angry at the declining death rate, for which he blamed Asklepios and complained to Zeus that Asklepios was responsible for it. Asklepios was subsequently worshiped as the doctor's divinity. The cult of Asklepios spread across all Greece and even to Rome by 293 B.C., with more than 200 temples.

During this same period, a more scientifically oriented medical philosophy was emerging. The more theoretical education held to the theurgical idea that illness was a divine punishment, but the nonpriestly assistants of the Asklepiads, whose large experience with patients allowed them practical observations, began to accept a more natural scientific way of thought. The initial medical school of importance established by these secularized Asklepiads was founded around 700 B.C. at Cnidos in Asia Minor. They completely abandoned theurgical medicine and based their diagnoses on bedside observations. A tumor was considered by them to be a malignant growth and not a visitation from some angry god.

Hippocrates

About 100 years later, this Cnidian school acquired a competitor on the nearby Aegean island of Cos (Fig. 6). The leader was a Greek physician named Hippocrates, who was born on the island of Cos about 460 B.C. and has since been honored as the "father of medicine". Some questions have been raised regarding the authenticity of the 72 medical works known as the "Hippocratic Corpus" or "Collection." Most scholars believe that Hippocrates wrote some of them and that a circle of doctors of Cos wrote some during his lifetime or shortly afterwards.[43,44]

The greatest significance of these Hippocratic writings lies in the fact that they repudiated the old theurgical and philosophic medicine and stressed the naturalistic approach, with great emphasis on observation of disease processes. Accordingly, medicine was considered a systematic science. Internal medicine was combined with surgery, and, in fact, the books on surgery in the *Corpus Hippocraticum,* believed to be the very ones written by Hippocrates, are generally regarded as its best section. His meticulous attention to details is evident from the following quotations from Hippocrates's writings on surgery: "What concerns surgery are the patient, operator, assistants, and instruments; the light. . . . The nails should be cut to the fingertips. A surgeon must learn to use his fingers through assiduous practice. The index finger and thumb are especially important. They must be trained in all kinds of work, individually as well as together: they should function well, elegantly, rapidly, easily, cleanly and immediately."[43] These books on surgery also indicate that

FIG. 6. Bust of Hippocrates. (Courtesy of the National Library of Medicine, Bethesda, MD.)

great skill was applied in the treatment of wounds, fractures, and dislocations, as well as in operations for fistulae-in-ano, hemorrhoids, trephining of the skull, and drainage of empyema. According to Allbutt,[45] "The chief lesson of the Hippocratic period for us is that, in practice as in honour, medicine and surgery were then one. The Greek physician had no more scruple in using his hands in the service of his brains than had Pheidias or Archimedes; and it was by this co-operation that in the fifth century an advance was achieved which in our eyes is marvellous [sic]. As we pursue the history of medicine in later times, we shall see the error, the blindness, and even the degradation of the physicians who neglected and despised a great handicraft."

Alexandria

The second great peak of Greek medicine was reached in the third century B.C. in Alexandria, which was founded by Alexander the Great after he defeated Darius III, the Persian king, and thus opened the way to Egypt. During this period, Aristotle, who was a teacher of Alexander the Great and founded his famous Lyceum, was a great creative thinker. He was especially interested in zoology and anatomy and often conducted dissections. He is considered to be the father of comparative anatomy, and his view of anatomic findings dominated medical thinking for 500 years, indeed until the time of Galen.

In addition, two important contributors to the Alexandrian school of surgery were Erasistratus and Herophilus.[18] The former, who studied and wrote on the heart and lymphatics, was interested in function, experimented in the field of digestion and circulation, describing the bicuspid and mitral valves, and apparently was aware of cardiac contractions and dilations. Herophilus was an able surgeon and contributed to the science of anatomy, with particular interest in the nervous system. He is generally considered the founder of anatomy.

The third peak in Greek medicine developed in Rome in the early centuries of the Christian Era and was symbolized by Galen.[46–49] Before Rome conquered Greece in 146 B.C., medicine and surgery had a low status in Italy for several reasons. For one thing, most of the doctors were Greeks, whom the Romans despised. A Roman citizen considered a doctor's work beneath him. This was clearly revealed by the note made by Pliny the Elder, that because Romans had gotten along without physicians for more than 600 years, they should be able to survive without "the cult of Aesculapius." He stated that, "Medicine is the only one of the arts of Greece, that, lucrative as it is, the Roman gravity has hitherto refused to cultivate. It is but very few of our fellow-citizens that have attempted it, and so soon as ever they have done so, they have become deserters to the Greeks forthwith."[50]

Celsus

Some Romans were willing, however, to write about the practice of healing, as, for example, Aulis Cornelius Celsus in his *De Re Medica Libri Octo* ("Eight Books on Medicine") published in 30 A.D., which provides an extensive picture of surgical art during the first century of the Christian era.[51] In his VIIth and VIIIth Books, there is evidence that surgery and midwifery had made considerable progress since Hippocrates and the Alexandrian School. Celsus described fully the techniques for lithotomy, piles, fistula, ulcer, fractures, luxations, excision of tumors, hernia repair, and certain plastic surgery procedures. Wound management was similar to that of Hippocrates. Ligatures were applied above and below the bleeding vessels, and amputation of larger limbs were done for the first time, but only in extreme need. He warned the surgeon not to use the suture until the depth of the wound had been cleansed and cautioned that no clot should remain, for this turns into pus, excites inflammation, and prevents union. He regarded surgery as an integral part of medicine and protested strongly against the tendency to separate them.

By that time, surgery was considered a science, not a handicraft. Celsus expressed the relatively high status of surgery thus: "And even in the cases where we count most on medicaments, it is evident not only that they often fail to restore health, but that health often returns without them. Whereas in the surgical branch of medicine, one can see that every successful cure, however supported to some degree by the other branches, is due primarily to the manual treatment."[51]

Galen

The most influential figure in ancient medicine besides Hippocrates was Galen (130–199 A.D.). For almost 15 centuries, Galen's views reigned over European medicine.[46–49,52–54] Not until 1543 did Vesalius rectify Galen's anatomic errors, and only in 1628, when Harvey discovered the circulation of the blood,[55] was Galen's faulty physiology abandoned. Galen's father, who yearned for the son to become a great doctor, sent him first to teachers of the Hippocratic school and then to medical school in Smyrna, Corinth, and Alexandria. In 158, on his return to Pergamon, he became physician to the gladiators and learned much practical surgery. In 162, he returned to Rome, where he again attended the gladiators, lectured actively, published profusely (more than 400 works), and became personal physician to the emperor, Marcus Aurelius.

Because autopsies were forbidden in Rome, Galen never dissected a human body. Instead, he based his anatomy on dissection of animals (Fig. 7) and was therefore sometimes in error. His physiology, based on his anatomy, was also, naturally, sometimes faulty. Yet his contributions to medical science cannot be gainsaid. He cautioned against cutting the laryngeal nerve and showed that urine flowed from the kidneys through the ureters to the bladder. Galen's surgery was based largely on the Hippocratic and the great Alexandrian anatomical and medical schools. He applied the ligature in amputations and stated that he obtained his "Celtic linen thread," which he used for this purpose, "at a shop in the Via Sacra between the Temple of Rome and the Forum," a shop near his own home.[45]

More important than his achievements in surgery, however, were those in pathology and internal medicine, a further refutation of the myth that all surgeons are traditionally technicians, not creative thinkers. His work was concerned with all phases of medicine, as well as surgery, with detailed instruction on the use of surgical tools. Within the range of his interest was the preparation of an anatomical treatise, more complete than any previously attempted, together with observations and speculation as to function. His physiologic views are based, in significant part, on actual animal experimentation and brought him additional fame as founder of experimental physiology.

Galen's tremendous posthumous influence, which dominated medicine for more than 14 centuries, can be ascribed in large part to the treatise entitled "On the Utility of Parts."[48] It carries the philosophic principles of Aristotle to the extreme, where it closely resembles a religious dogma, explaining that only a thoughtful Creator could have designed each part of the human body for the very function for which it was intended.

Galen's everlasting monuments were his remarkable scientific achievements and a large body of writings he left behind, including descriptions of surgical procedures on various parts of the body (Fig. 8). These became can-

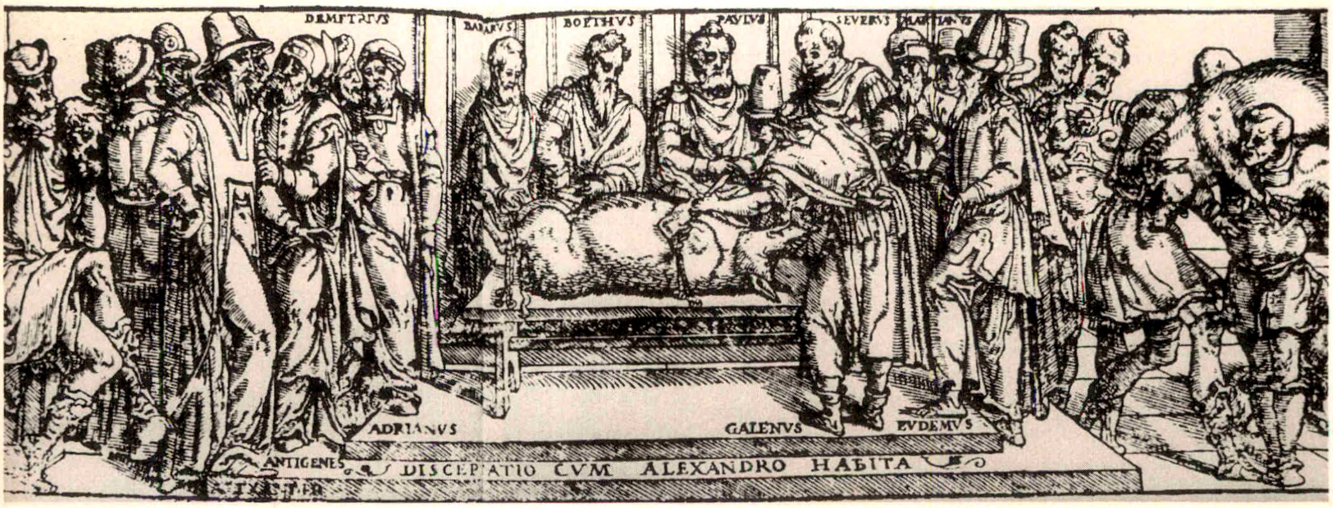

FIG. 7. Frontispiece of a collection of Galen's works published in 1565 showing Galen dissecting a pig. (Courtesy of the National Library of Medicine, Bethesda, MD.)

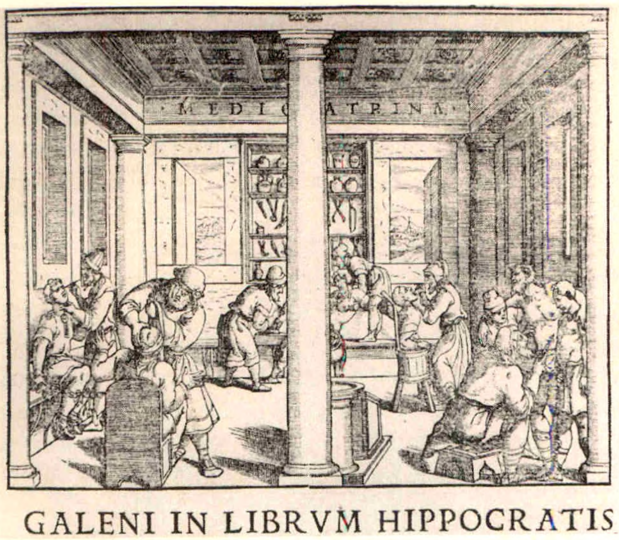

FIG. 8. Clinic scene from the Venetian editors of Galen's works published in 1550, showing surgical procedures described by Galen on the head, eye, leg, mouth, bladder, and genitals. (Courtesy of the National Library of Medicine, Bethesda, MD.)

onized in later centuries to the point that disagreement with them was tantamount to heresy, and the posthumous reverence extended to him far surpassed his contemporary fame. The concomitant arrest of all medical thinking to conform with Galenical concepts seriously impeded scientific progress.

Although Galen was the dominant figure of his era in all of medicine, one of his contemporaries, Antyllus, assumed an important role in the field of surgery. Little is known about his life except that he lived during the first half of the second century A.D. His works have been lost, but they are presented in the writings of Oribasius.[56] Obviously a highly skilled and experienced surgeon, he gave precise description for a number of individual operations. Moreover, he gave specific direction regarding the indications and contraindications, as well as complications, of operations. Among these operations were tracheotomy, extraction of cataracts, fistulas, phimosis and hypospadia, and plastic surgery for alleviation of defects on the eyelids, ear, and nose. His operation for aneurysm was his most remarkable achievement; it remained the standard procedure for 16 centuries, indeed, until it was modified by Hunter and Matas. The operation consisted of ligating the artery above and below the aneurysm and then opening the aneurysm and evacuating its contents. He gave detailed and precise instruction concerning its performance. He also advised against operating on certain types of aneurysm of large volume but recommended the procedure for aneurysms in the extremities. Another important surgeon during this period was Soranus of Ephesus, whose treatise on "Diseases of Women" is regarded as a classic.[57]

Byzantine Surgery

The Byzantine Empire began in 330 A.D. after the Roman Emperor Constantine the Great made Byzantium the capital of the Roman Empire and renamed it Constantinople. This period came to an end in 1453, after the Turks captured Constantinople, later named Istanbul.

Byzantine medicine (and surgery), which derived from the Greeks, contributed greatly to medieval scholarship.[20] The first to compile an encyclopedia of Greek medicine was Oribasius (325–403 A.D.), personal physician to Julian the Apostate. The 70 volumes of his *Synagoge* comprised the best in Greek and Roman medicine.[56]

Although the status of surgery was not greatly enhanced during this period, there is some evidence that it did not regress. Indeed, reports of some technical procedures reflect reasonably good knowledge of anatomy and bold adventureousness. This is demonstrated by the writings of Aetius of Amida, during the seventh century on *De vasorum dilatatione* (On the Dilatation of the Vessels), which is now in the Vatican Library.[58,59] It deals with aneurysms and suggests that the author had some knowledge of the Antyllus operation, as evidenced by the following passage:

> An aneurysm located in the bend of the elbow is treated thus. First we carefully trace the artery leading to it, from armpit to elbow, along the inside of the upper arm. Then we make an incision on the inside of the arm, three or four finger-breadths below the armpit, where the artery is felt most easily. We gradually expose the blood-vessel and, when it can be lifted free with a hook, we tie it off with two firm ligatures and divide it between them. We fill the wound with incense and lint dressing, then apply a bandage. Next we open the aneurysm itself and no longer need fear bleeding. We remove the blood clots present, and seek the artery which brought the blood. Once found, it is lifted free with the hook, and tied as before. By again filling the wound with incense, we stimulate good suppuration.[58]

Paul of Aegina (607–690), the last of the classical Byzantine physicians, was a contemporary of emperor Heraclitus I and wrote an *Abridgement of Medicine in Seven Books,* which remained a bible for surgeons for a long time.[60] Translated into Arabic, it was the basis of the Arabian age of medicine, and leading Arab writers like Albucasis adopted almost verbatim Paul's sixth book, on surgery.

In his historical assessment of Byzantine surgery, Bliquez[61] stated that the Byzantines were generally considered to have originated little but to have passed on a great deal. His own studies of Byzantine surgery bore out this conclusion. The fact is that dissection of the human body was practiced continually, suggesting that surgeons were directly acquainted with human anatomy, and this, according to Bliquez, was probably a significant factor in preventing Byzantine surgery from sliding backward. A careful review of the surgical instruments representing this period provided Bliquez with "the firmest evidence at hand that most of the major surgical tools employed by Paul and his predecessors (and therefore most of the operations for which they were used) were in use from at least the Macedonian dynasty through the Comneni. It appears, therefore, that the state of surgery did not decline significantly in the Middle Byzantine Period. It may be that in some respects it even advanced a bit."[61]

A final commentary about the Byzantine Period is concerned with the development of hospitals beginning in the third century and evolving into a well-organized structure and facility for the care of the sick.

In a letter addressed to the Governor of Cappadocia, in Asia Minor, Bishop Basil of Caesarea (370–379) referred to several lodges or inns that he had built outside his city to serve strangers, both those passing through and those needing care for illness. Basil hired nurses and doctors.[62]

John Chrysostom, Bishop of Constantinople (398–404) opened similar institutions in the capital. His biographer, Palladios, called these philanthropic houses "*nosokomeia*," places to care for the sick. To staff them, John appointed two priests as directors and hired physicians, cooks, and servants. Although Palladios adds that these institutions served both those stricken with disease and the strangers, the term *nosokomeion,* derived from *nosos* (disease), suggests that the care of the sick predominated in these foundations. According to Miller,[62] by the end of the fourth century, philanthropic Christian institutions began offering hospital services to the poor. Within the next several centuries and by the reign of Justinian, hospitals stood at the center of the medical profession in the Byzantine Empire. Staff physicians, including surgeons, were assigned to these hospitals and had a hierarchal order. They also had time for private practice.

Arabic Period

With the disintegration of the Roman Empire and the rise of the political and military power of Islam, the Mohammedan Empire, beginning in the seventh century, spread through the Near and Middle East into North Africa, Spain, and part of France and assumed cultural leadership in virtually all fields of endeavor, particularly philosophy, mathematics, science, and medicine. This leadership it maintained until the Renaissance. The Arabs had inherited much Greco-Roman knowledge and culture well before the founding of Islam. As early as 76 A.D., Jews had fled to Arabia when the Romans destroyed Jerusalem. In the fifth century, the Nestorian Christians, who had been expelled from Constantinople in 431 A.D., had settled in Edessa in Mesopotamia but later were driven away to Gundishapur in Persia (where they founded another hospital).[63]

Some historians have stated that Arabic medicine "contributed no original or novel ideas"[22] and served principally as compilation and preservation of their GrecoRoman inheritance. Because surgery was held in low esteem, its status declined and many of the surgical procedures used at that time, such as cutting, bandaging, cauterizing, and cupping, were performed by untrained laymen or folk doctors and charlatans. Of interest is the statement made some centuries later by Guy de Chauliac that ". . . one finds that until [Avicenna] . . . all were physicians and surgeons combined, but since then, whether because of delicacy or because of too great a preoccupation with cures, surgery has become separated and abandoned to the hands of mechanics."[64]

The fact remains, however, that there were some outstanding physicians who practiced surgery and wrote about their observations and experiences. Among these the most important were Rhazes[65] and Avicenna[67] in the eastern caliphate and Albucasis,[68] Avenzoar,[69] and Maimonides[70] in the western caliphate. Abu Bakr Muhammed ibn Zakaria Al Razi (852–925), known as Rhazes, wrote brilliant, and perhaps the first accurate, descriptions of measles, smallpox, and other diseases.[66] Although his medical views were influenced by Hippocrates and Galen, his erudition was broad and deep, and he demonstrated considerable originality. His *Al Hawi* was a 25-book encyclopedia of medicine and surgery.[65]

Perhaps the most influential Arabic contributor to medicine was Avicenna (abu-Ali al-Husayn ibn-Sina, 980–1037), whose status in Islam as well as Christendom was equal to that of Galen. He was apparently a boy prodigy, having mastered the Koran at the age of 10 years, and he wrote a scientific encyclopedia at twenty-one years. The most famous of his approximately 100 books was *The Canon* (Al-Qanun) (Fig. 9), which constituted the basis for medical ideas and procedures as well as the curriculum for Christian universities for hundreds of years, indeed until the mid-17th century. Unfortunately, his attitude toward surgery—a necessary evil—remained popular and probably helped to influence the decline of surgery.

Perhaps the most important Islamic surgeon was Albucasis (Abul Qasim al-Zahrawi, 936–1013), whose encyclopedic *Al Tasrif* (The Method), the first illustrated and systematic text, greatly influenced the Christian West.[68] Guy de Chauliac (1300–1380), for example, used some 200 quotations from him. His work contained many illustrations of surgical instruments, and he was obviously a skilled surgeon who advanced the teachings of Paul of Aegina and others. He embraced surgery as a worthy art, revealing a cautious, ethical, and thoughtful approach, in contradiction to the prevalent attitude of Arabic medicine to relegate surgery to an inferior status.

Although the preservation of Greco-Roman medicine was the greatest contribution of Islam to medicine, the Islamic thinkers and the Christians, Persians, Jews, and others who lived in the Mohammedan Empire (sometimes referred to as "Arabists" because their writings were

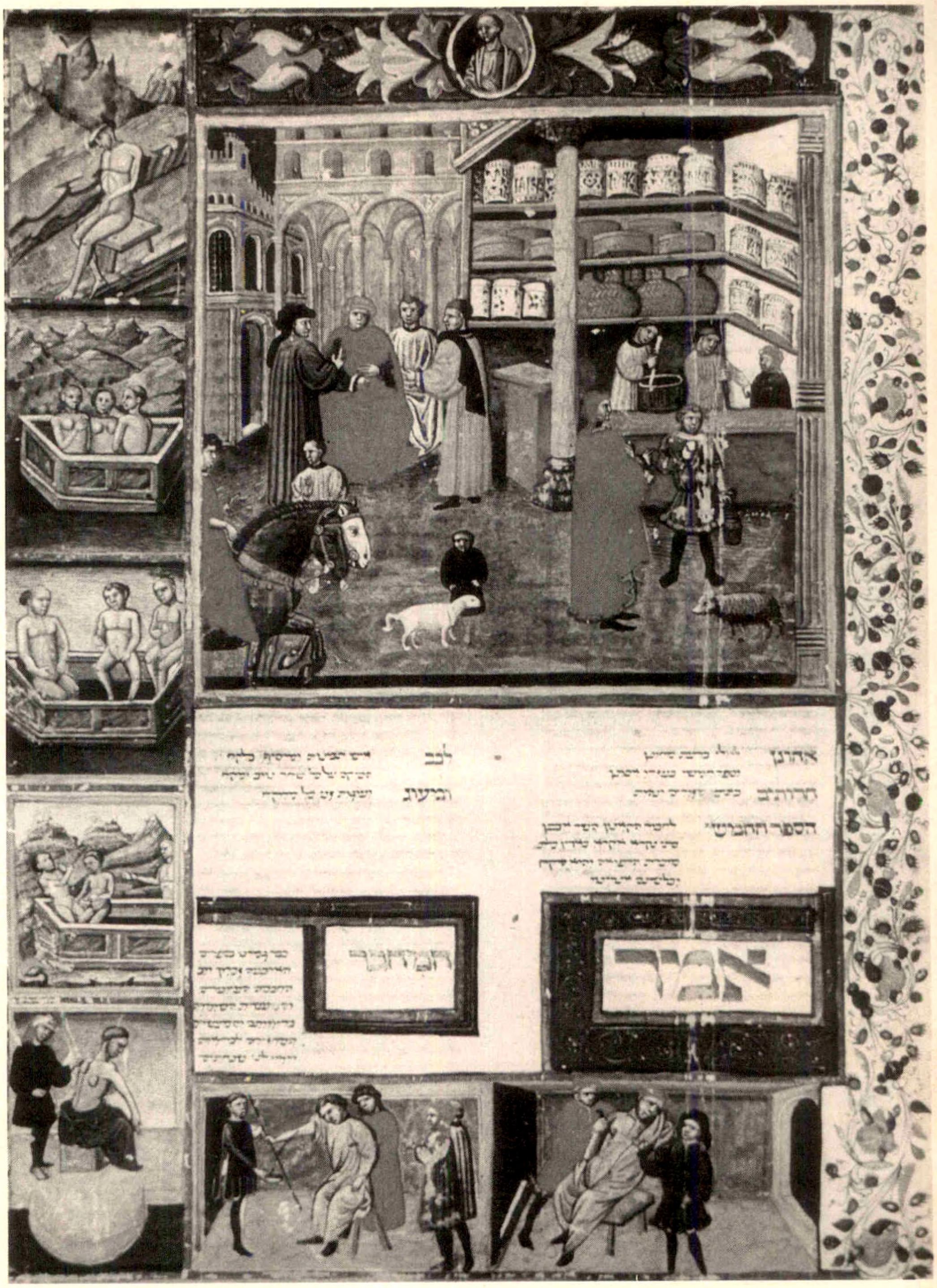

FIG. 9. *Canon* of Avicenna. (Courtesy of the Biblioteca Universitaria, Bologna, Italy.)

mostly in Arabic) added much to their Greco-Roman heritage. Through their translations, they bridged Arabic and Latin learning and thus returned Greek work to the Christian West. Another and equally important contribution of Islamic medicine was its establishment of the hospital system. Whereas there were a few Christian hospitals in the West compared to the Islamic hospitals, they were inferior in facilities, organization, sanitation, and medication. Among the best Islamic hospitals were those at Baghdad (9th and 10th centuries), Damascus, and Cairo. Rhazes taught and practiced in the hospital in Baghdad, where he collected clinical reports for teaching. The hospital-medical school in Damascus was known for its elegant rooms and extensive library. The Al-Mansur

Hospital in Cairo, founded in the 13th century, was considered the largest and most magnificent, with separate wards for different diseases.[71]

Medieval Medicine (476–1453)

The Medieval period or The Middle Ages (also sometimes called the Dark Ages) spanned the millenium, beginning, according to most historians, with the fall of Rome to the Goths in 476 and ending with the fall of Constantinople to the Turks in 1453, or when printing was discovered in 1440. Although some great constructive activities occurred during this period, as exemplified by the building of great cathedrals in Europe and the founding of great universities, in science and medicine there was progressive deterioration of the intellect.

The decline in medicine and particularly in surgery has been attributed to a number of factors. Included among these were the unsettled conditions of this period as a consequence of marauding conquerors and warring factions that produced a longing for certainty and authority.[72] This was met to a large extent by the rising domination of the church producing what some historians term "the Age of Faith." Although Galen was not a Christian, his teleologic reasoning was embraced readily by the Christian Church. Moreover, his dogmatic, didactic, and pedantic style, along with his encyclopedic codifications integrating all previous knowledge, provided a ready source of medical information. In addition his name was enshrined by subsequent compilers and commentators of high repute such as Oribasius,[56] Aetius,[58,59] Alexander of Tralles,[73] and Paul of Aegina.[60] With the Church crushing any opposition to its dogma and the acceptance of Galen as the fountainhead of all medical knowledge, new ideas were considered heresy, and so religious medicine returned, with illness interpreted as retribution from heaven. Since the cure depended on God's will, operations did not seem worthwhile. Autopsies were absolutely forbidden, and hygiene was nonexistent. Surgery suffered tremendously.

Christ's healing mission became institutionalized, and in some areas such as Paris, rigidly fixed by sacrodotal scholastics, it was to control medical care for centuries. In the statutes founding his order at the monastery on Monte Cassino (on the site of the ancient temple of Apollo), St. Benedict of Nursia encouraged the care of the sick, but because the cure of disease was possible only through prayer and divine intervention, St. Benedict forbade the study of medicine.[22]

Still another important factor that influenced the decline in the status of medicine (and surgery) was the hagiolatry that characterized the early part of the Middle Ages and was subsequently strengthened by the Church. Indeed, miracles became an important mainstay of the growth and development of the Church, and those deemed to be particularly holy were considered intercessors for these actions. While St. Luke was himself a physician, the most famous of all medically inclined saints were probably St. Cosmas and St. Damian, Arab twins who became the special patrons of surgery because of their miraculous operations.[74–77] One legend was that they appeared posthumously to amputate a cancerous leg and replaced it with one taken from a Moor who had just died (Fig. 10). This feat has been portrayed many times by artists such as Andrea Mantegna and can be seen today in the *Antiphonarium S. S. Cosmae at Damiani* in London. Later in the Middle Ages, there developed an increasing number of saints associated with relief from a single disease or condition. Thus, St. Christopher, considered a patron of travelers, also was called on to deal with the plague and sudden death; St. Anthony gave protection against erysipelas; St. Margaret of Antioch became the patron of women in childbirth; St. Erasmus offered protection against seasickness and stomach ulcers.

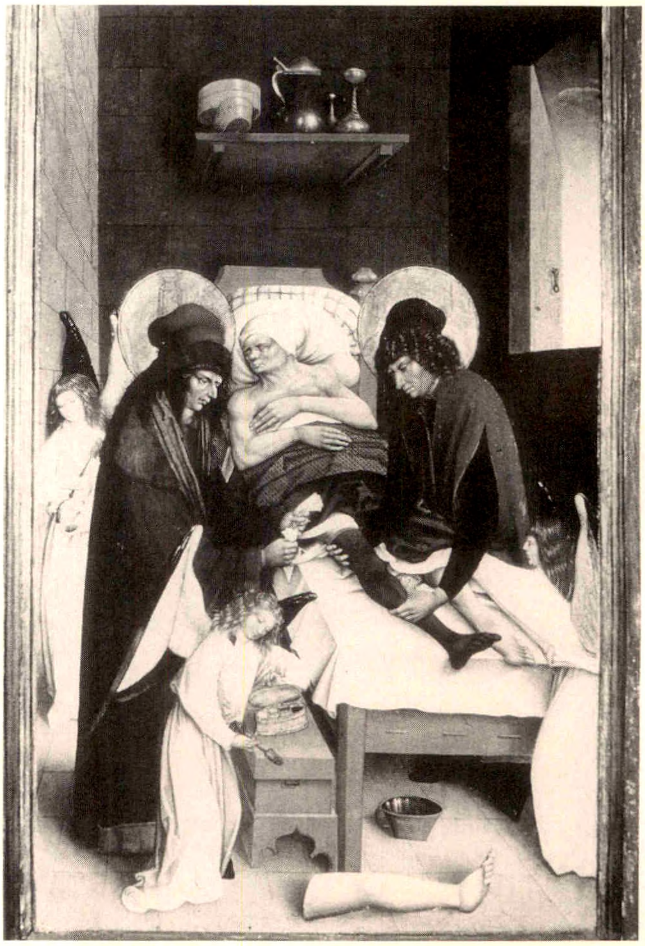

FIG. 10. Sts. Cosmas and Damian, the martyred Arab twin physicians, performing the famous posthumous miracle: replacement of a sacristan's gangrenous leg with that of a dead Moor. (Courtesy of Dr. James Young.)

The Salerno School

In western Europe during the Middle Ages, medicine in general and surgery in particular assumed low status. For this reason, the establishment of the Salerno School, or *Civitas Hippocratica* as it became known, assumed great significance.[78] Although the exact date of its establishment is uncertain and although the legend concerning its origin is probably apocryphal, there is recorded evidence that it had become highly regarded by the ninth century. Differing from almost all other universities, it was purely secular and therefore not under ecclesiastic control. Its rapid expansion and flowering during the 12th century was encouraged by the wisdom of its rulers after the Norman conquest of southern Italy.[79–81]

The medical students at Salerno received training in medicine and surgery, although the period of time was longer for medicine. A small group of these students completed the entire course of medicine and then became surgeons. Since there were few places in the medieval world where this combination occurred, there were only a few university-trained surgeons, among them Hugo of Lucca,[19] Theodoric,[82] William of Salicet,[83] Arnold of Villanova,[84] Lanfranc,[85] and Pitard.[86] Although Hugo of Lucca left no written record of his work, his achievements are known from the writings of his disciple, Theodoric (1205–1296), who was thought by some to have been his son. Although the university-trained surgeons were few, they constituted the basic development of European Surgery and thus enhanced the status of surgery.

The secular medical school established at Salerno flourished from about 1000 A.D. until the 13th century. Probably the first legitimate degree for physicians, which was introduced by Roger II, was awarded by this school. His grandson Frederick II, Holy Roman Emperor, established an examination with standards of knowledge that ranked medicine together with surgery. Surgery, having been reduced to a lowly handicraft under earlier Roman and subsequent Arabian domination, now entered rehabilitation. Not only had the Arabs lacked interest in surgery, but the European priests, according to canon law, immediately lost their jobs if they caused anyone's death during surgical treatment, and therefore were frightened from operating.

One of the men who helped develop the Salerno School into the leading European center of medical education was Constantine, known as "Africanus." His translations of Greek and Arabic texts into Latin fashioned the Salerno School's curriculum, and thus spread Arabian medical knowledge, as well as that gained from the classic Greco-Roman period, to the West. The only other educational center of similar repute was Montpellier in France, near the border of the Arabs' western caliphate. The 20 volumes of the "Royal Book," *Al-Maleki* by Ali Abbas, a handbook of all of medicine, was called *Pantegni* ("The Total Art") by its translator, Constantine.[87] Constantine revived Hippocrates and Galen, long forgotten in Italy.

The teachers of the Salerno School began producing their own writings, at first about internal medicine and medical ethics, in the Arabian tradition. Of great significance were the surgical books produced at Salerno, based primarily on the surgeons' personal experiences. Although they still did not dare dissect human bodies, they studied the anatomy of pigs, and they observed the findings of the otherwise spurned cataract-knitters, hernia-carvers, and lithotomists. From a combination of these clinical skills, clinical knowledge, and lessons from Greece and Arabia developed a sound surgery, and Salerno became the cradle of modern Western surgery.

Salerno's first great surgeon was Ruggiero Frugardi (Roger of Salerno), who wrote *Cyrurgia Rogerii*[88] (1170 A.D.) (Fig. 11), called the first independent surgical work in the Western world. The book spread throughout Europe.

Salerno's Successors

After Roger's death, medical leadership moved from Salerno to Bologna, with its large university. The medical school's founder, Ugo di Borgognoni, sometimes called Ugo or Hugo of Lucca (1160–1257),[19] and his disciple Theodoric (1205–1296), denied that healing of wounds required pus formation, as promulgated by Roger and his apprentice Roland. "Such a practice," Theodoric maintained in *Chirurgia* (1267), "is indeed to hinder nature, to prolong the disease and to prevent the conglutination and consolidation of the wound."[82]

The other most important surgical text of this period, besides that of Roger of Salerno, was the *Cyrurgia* by Guglielmo da Saliceto, known as William (1210–1280),[83] who argued that any distinction between medicine and surgery was absurd: the surgeon was merely a doctor who treated with his hands.

Three Great Frenchmen

Guido Lanfranchi, known as Lanfranc (d. 1315) (Fig. 12), the founder of surgery in France, was born in Milan and educated by William of Saliceto. In 1295 he moved to Paris, having been driven from Italy by the urgencies of civil war, and became affiliated with the independent college of Saint-Côme, which, according to historians, was established around 1240 and was independent of the University of Paris. Subsequently, it became the examining body for the lay surgeons of Paris. By bringing to France the great attainments of Italian surgery, he advanced French surgery toward leadership for several centuries. He finished writing his *Chirurgia magna* in 1296.[85] Additional evidence that Lanfranc's influence in the en-

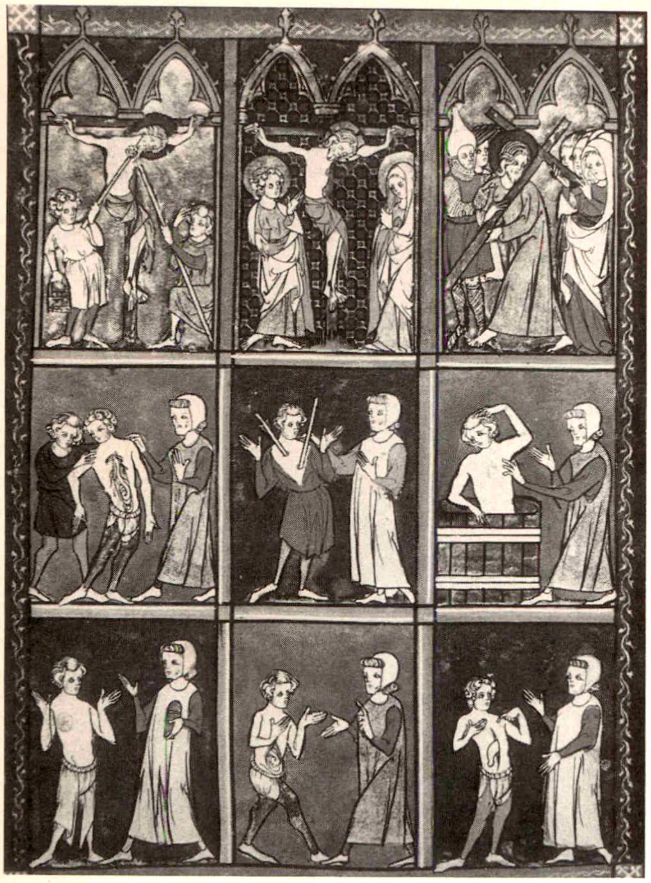

FIG. 11. A page in the manuscript of Roger of Salerno's *Chirurgia* showing various treatments of wounds. (Reprinted with permission from the British Library, London, UK.)

hancement of surgery went beyond the borders of France is exemplified by one of his pupils, a Flemish physician named Yperman, who subsequently became known as the father of Flemish surgery and, like Vesalius, holds a special place in Belgian medicine. In his *La Chirurgie,*[89,90] Yperman followed the teachings of Lanfranc and described in detail the indications and technique of ligature of arteries. Lanfranc subscribed to his mentor William's view: "Oh Lord," he wrote, "why is there so great a difference between a surgeon and a physician? But the philosophers have taken the craft in laymen's hands. Or as many men have disdain for to work with their hands. And yet many men ween that it is impossible for one man to know both the crafts. But thou shalt know well this, that he is no good physician that knows nothing of surgery, and the contrary thereof, a man may be no good surgeon if he knows no physic."[91] He became the personal physician of Philip the Fair, a post that was next filled by one of France's most illustrious surgeons, Henri de Mondeville (1261–1320).[92]

A student of Theodoric's, Henri carried further his mentor's doctrine about the care and hygiene of wounds. Like Theodoric, he vigorously denounced the concept of "laudable pus," despite severe criticism. In his instruction on wound management, he emphasized washing the wound to remove all foreign matter and to avoid applying oily or irritant matters. "Wounds," he stated, "dry much better before suppuration than after it."[45] He cautioned against the cautery for control of hemorrhage, and for large vessels he advised the use of the ligature. Unfortunately, the vigorous message of Theodoric and Henri concerning wound management and the promotion of healing by first intention went unheeded and the "advocates of suppuration won all along the line; and for centuries to come poultices and grease were still to be applied to fresh wounds; and tents, plastered with irritants to promote suppuration, were still to be thrust into the recesses of them, even when there was no foreign matter to be discharged."[45] His book *Chirurgie* (?1306–1320) was the first surgical textbook by a native Frenchman and made France the world leader in surgery. Henri, while acknowledging that many of Galen's teachings were correct, asserted that "God surely didn't use up all genius on Galen."[45]

LANFRANC.
Professeur en Chirurgie à Paris,
au treizieme Siècle.

FIG. 12. Wood engraving of Lanfranc. (Courtesy of the National Library of Medicine, Bethesda, MD.)

The third great medieval French surgeon, Guy de Chauliac (d. 1368), produced a textbook, *La Grande Chirurgie,*[64] which, except for that of Hippocrates, was proclaimed to have no other of equal value. Both Garrison[10] and Allbutt[45] have accused Guy de Chauliac of retarding the management of wounds for centuries by his rejection of the nonsuppuration methods, but this view is not shared by Zimmerman and Vieth,[20] nor, according to them, by his definitive biographer, Nicaise.[64] A careful reading and interpretation of his chapter on wounds suggests his general support of primary intention, his indications for the use of sutures and bandages, as well as the indications for drains and packs. During Guy de Chauliac's residence in Avignon, the Black Death struck in two epidemics, and to his credit and that of other surgeons, he stayed and cared for the victims of the plague when most of the physicians fled. His graphic description of the epidemic, which appears under the title, "The Great Mortality of 1348 and 1360," is one of the earliest records of the ravages of the bubonic plague. Guy himself contracted the disease, as he described, but recovered after 6 weeks. The methods of Guy de Chauliac dominated surgery in France until Vesalius and Paré revised them some 200 years later.

Influence of the Church

As previously stated, the decline in the status of surgery in medieval Europe has sometimes been attributed to the Church. Even in pagan Rome, however, there was a tendency to separate medicine and surgery, with the latter being considered a lower caste occupation. Certain attitudes and policies of the Church, however, were said to exert a demeaning influence on the practice of surgery. Although some historians have contended that surgery was forbidden to the clerics by the Council of Tours (1163) on the basis that, "The Church abhorreth bloodshed" (*Ecclesia abhorret a sanguine*), de Moulin labeled this Latin phrase "a literary ghost," since it could not be found in the text of the Council of Tours.[93] A binding prohibition to that effect, however, was detailed by the Fourth Lateran Council in 1215, as well as the Council of Nimes (1284), Wurzberg (1298), and Bayeux (1300): "Let no subdeacon, deacon, or priest exercise any act of surgery which extendeth to cautery or incision."[18,45,93]

Barber-Surgeons

The significance of these policies and edicts lies in the fact that, more often than not, the institutions in which an education could be obtained were operated by the Church. Thus, in the medical school of the University of Paris, surgical instruction was inhibited. This ultimately led to a professional caste system in Paris, consisting of physicians, surgeons of the long robe (licensed by the College of Saint-Côme), surgeons of the short robe or barber-surgeons (Fig. 13), and lithotomists or oculists. The introduction of the barbers into the hierarchy of medicine appears to have had its origin with the ecclesiastic custom that required shaving of the crown of the head and later periodic, and supposedly prophylactic, phlebotomy. After the College of Saint-Côme, which was founded by a confraternity of surgeons in Paris and named after St. Cosmas, obtained the privilege of surgical licensure, the physicians, jealous of the growing influence of this group, encouraged untrained barbers as creatures of their own and even hired them to perform various procedures, such as routine "prophylactic" phlebotomies so popular at that time, tonsorial work, and operating baths. These barber-surgeons were called surgeons of the short robe in contrast to the surgeons of the long robe.

A surgeon of the short robe, and barber of King Charles V (Charles the Wise, 1337–1380), who was master of the guild of barbers, persuaded the King to issue an edict permitting them to treat wounds and sores and forbidding surgeons to interfere with them. The relative status of these three kinds of medical practitioners is reflected in the following order issued by King Charles V during an epidemic of the pest in 1383: There "shall be selected to visit the sick four physicians, two surgeons, and six barbers, and the fees of the doctors shall be three hundred livres, of the surgeons one hundred and twenty livres, and of the barbers eighty livres."[5] It is thus apparent that there is nothing new or original in the current concept of the Resource-Based Relative-Value Scale (RBRVS) promulgated by the Harvard School of Public Health.

Medieval English Surgeons

John of Mirfield, chaplain at Saint Bartholomew's Hospital in London, was also a librarian and an unschooled, amateur doctor. His *Breviarium Bartholomei,* a collection of original works by authorities such as Galen and Guy de Chauliac, was interspersed with his own notes about treatment and prognosis. In his *Florarium Bartholomei,* he pointed out, like Lanfranc in France, the fallacy of making a distinction between physicians and surgeons: "Long ago, . . . physicians used to practice surgery, but nowadays there is a great distinction between surgery and medicine, and this, I fear, arises from pride, because physicians disdain to work with their hands, though, indeed, I myself have a suspicion that it is because they do not know how to perform particular operations; and this unfortunate usage has led the public to believe that a man cannot know both subjects, but the well informed are aware that he cannot be a good physician who neglects every part of surgery, and, on the other hand, a surgeon is good for nothing who is without knowledge of medicine."[94]

The disdain for surgeons, however, persisted in England longer than anywhere else, and even today the tradition

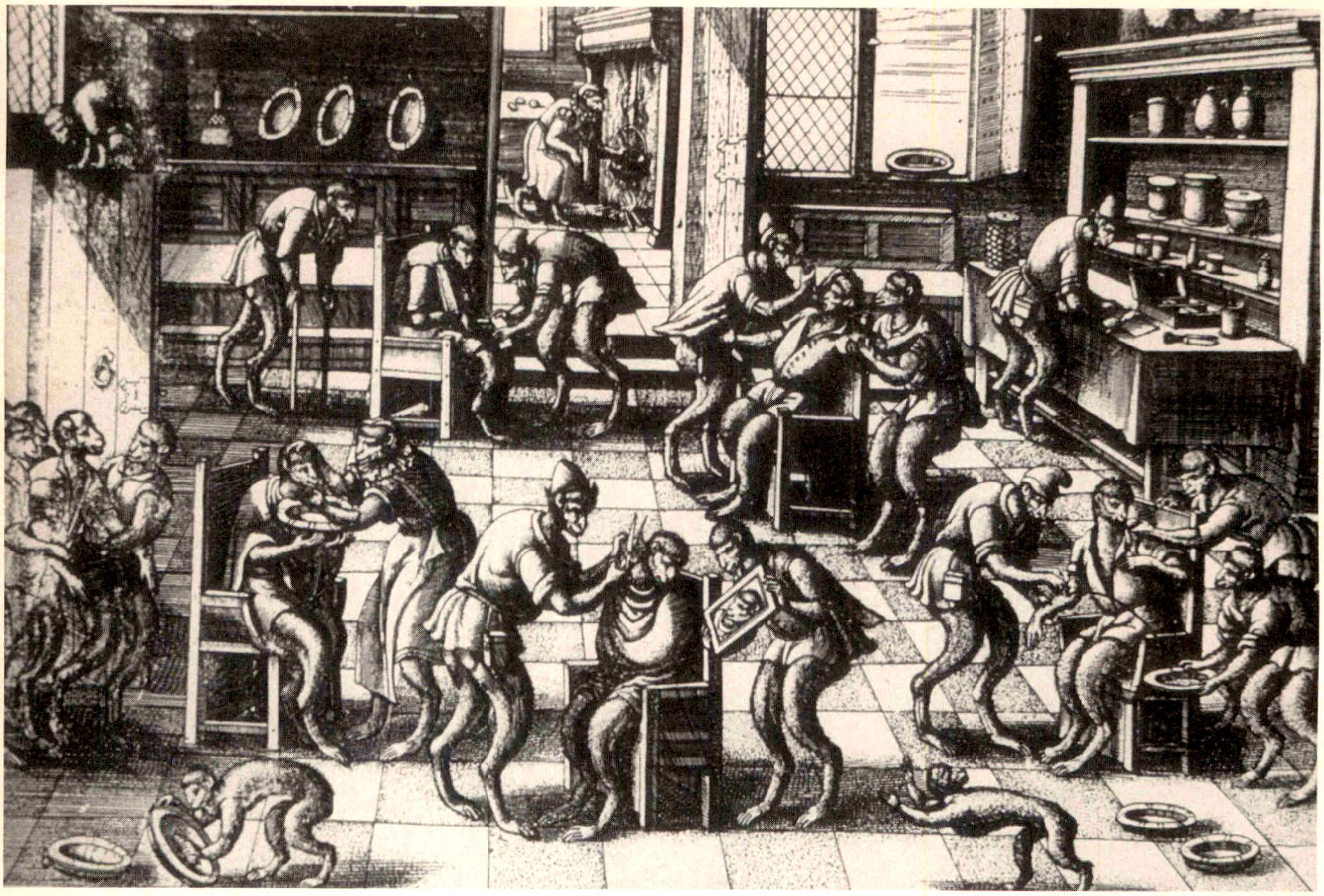

FIG. 13. Photograph of a 16th century engraving that satirizes doctors as monkeys performing a variety of duties by barbers such as tooth pulling, hair cutting, blood letting, and wound treatment. (Courtesy of AS Lyons and RJ Petrucelli,[22] Harry N. Abrams, Inc., New York, NY.)

of addressing physicians as "Doctors" but surgeons as "Misters" remains. Interestingly, British surgeons now regard "Mister" as an honorific title.

England's first important surgeon was John of Arderne (1306–1390), the world's first proctologist.[95] He gained considerable surgical experience during the Hundred Years War and was actively engaged during the Seige of Algiers against the Moors when, for the first time, gunpowder was used. In his practice he included the whole of surgery but became particularly interested in diseases of the rectum. Following his move to London, he was admitted to the Surgeons' Guild as a Master Surgeon. His *Treatises of Fistula in Ano, Hemorrhoids and Clysters* was his most important contribution to surgery.

Surgery in the Renaissance

The 15th century in Europe was marked by a fresh look at many aspects of life. Criticism and revision flourished. Antonio Benivieni (1440–1502) grew wealthy from his practice of surgery and kept careful notes on his patients, with follow-ups from autopsies. In 1507, his friend Rosati published these notes as *De abditis morborum causis* ("The Hidden Causes of Illnesses").[96] Much new information about pathology thus became known that was of great value to surgeons. Some referred to the book as "the end of the old humoral tradition."[20]

The first Pope to approve autopsies was Sixtus IV (1414–1484), who, by this act, stimulated further study of the structure of the human body.[21] A further stimulus was provided by artists, who rejected the stylized Gothic portraits of the 15th century in favor of greater reality. Donatello and Pollaiuolo were among the first artists to study anatomy of the human body by dissection, followed by Leonardo da Vinci, Michelangelo, Dürer, and Titian. Da Vinci (1452–1519) left 779 anatomical drawings, among which was a precise drawing of transverse veins in the lower leg, now at the archive of Windsor Castle. The theater of anatomy at Padua, built in 1446, allowed Vesalius to teach, Realdus Colombus[97] to describe pulmonary blood circulation, and William Harvey[55] to participate in dissections.

After the Alexandrian school, the Italian school showed early appreciation of anatomy. Thus, approximately two centuries before Sylvius in Paris was teaching anatomy, Mundinus (Mondino de Luzzi, 1275–1326) was reviving the study and teaching of anatomy at the University of Bologna, where he also practiced surgery. The combination of professorship of anatomy and surgery continued at Bologna for 250 years. Mundinus's *Anathomia,*[98] written in 1316, was considered an essential manual of anatomy and dissection for two centuries until displaced by Vesalius's *Fabrica.*

Jacob Sylvius (1478–1555) in Paris, considered the first great anatomist of the Renaissance, accepted Galen's anatomy unreservedly.[97] Among his many students was Andreas Vesalius (1514–1564). Born in Brussels and educated at the University of Louvain, he went to Paris, where he studied under Sylvius. Later he went to the University of Padua, where he obtained the degree of Doctor of Medicine "with highest distinction." On the following day, at the age of 23 years, he was appointed Professor of Surgery. His duties in this position included the teaching of anatomy and holding of public dissections. During the next 5 years he worked on the monumental task of preparing an entirely new book of the complete anatomy of the human body based on his personal dissections and was able to enlist an excellent artist, Jan Stefan van Kalkar, also a native of Flanders and Titian's favorite pupil.[20] Entitled *De Humani Corporis Fabrica* (Fig. 14), the seven books were published in Basel in 1543, when the author was 28 years old.[99]

There ensued a fervent academic controversy between Vesalius and almost all the rest of the medical world, with Sylvius heading the opposition. Embittered and disillusioned by these attacks, Vesalius retired from further academic pursuits and began practicing surgery, serving in several military campaigns. In the preface to his book addressed to "The Divine Charles V," the Emperor of Spain, whose physician he became after resigning his chair at Padua, he expressed his resentment and obvious bitterness against the physician's attitude toward surgeons as follows: "Thus in course of time the art of healing has been so wretchedly rent asunder that certain doctors, advertising themselves under the name of physicians, have arrogated to themselves alone the prescription of drugs and diet for obscure diseases, and have relgated the rest of medicine to those whom they call surgeons and scarcely regard as slaves, disgracefully banishing from themselves the chief and most ancient branch of the medical art, and that which principally (if indeed there be any other) bases itself upon the investigation of nature."[100]

In 1564, at the age of 50 years, while returning from a pilgrimage to the Holy Land, he was shipwrecked on the tiny Peloponnesian Island of Zante, where he died. The reason for this pilgrimage, according to Major,[19] lies in the fact that when Vesalius opened the chest of a Spanish nobleman who had died in his care, he found the heart beating and the parents accused him of murder and brought in the Inquisition. The King intervened and had the punishment commuted to a journey of penitence to the Holy Land.

Vesalius's remarkable textbook of anatomy, considered among the greatest of all medical texts, not only revolutionized surgery but greatly stimulated the development of physiology and pathology, as well as anatomy.

From Barbers to Paracelsus

As occurred earlier in France, the caste system among medical practitioners in England became embroiled in the effort to achieve separate status. Accordingly, before 1369, the surgeons organized "The Guild of Surgeons Within the City of London," whose purpose was to separate themselves from the barbers, but it was not very successful in persuading people that surgeons were the equal of doctors.[101] Doctors of internal medicine, known as herbalists because they prescribed mainly healing plants, continued their conflict with surgeons about a new regulation regarding the right to practice medicine professionally. The herbalists won, and the surgeons became covered by a rule that placed them on the same level as bakers, brewers, and public notaries. The surgeons reacted by affiliating themselves with barbers again.

Surgeons and barbers worked side by side, if not too harmoniously, in the army of Henry V at Agincourt (1415), and it was not until two centuries later that Henry VIII established some order in the relationship by uniting the barbers and surgeons by an Act of Parliament of 1540, made famous by Holbein's painting (Fig. 15).[102] Thomas Vicary (1490–1562),[94] "sergeant-chyurugeon to King Henry VIII," became the first master surgeon. This Company of Barber-Surgeons continued until 1745, when it became organized as the Company of Surgeons. In 1800, it became the Royal College of Surgeons of London, and in 1843 the Royal College of Surgeons of England.[102]

Philippus Aureolus Theophrastus Bombastus von Hohenheim (1493–1541) (Fig. 16), a controversial figure in his time, has been called one of the great medical innovators of the Renaissance. Immodestly, he called himself Paracelsus—or the equal of the Roman physician Celsus. Born in Switzerland, he traveled extensively, although there is no evidence that he ever studied medicine or had a right to the title of doctor, but he apparently learned much from conversations with doctors, pharmacists, and chemists. At Basel, he was made professor of medicine, as well as city doctor, in 1527. His main thesis was not to rely on books but on the doctor's own experience and on nature's teachings (Fig. 17). In *Grosse Wundartznei,* he wrote: "Internal medicine and surgery are based on philosophy and must not be separated except in practice; every physician must be a doctor of both

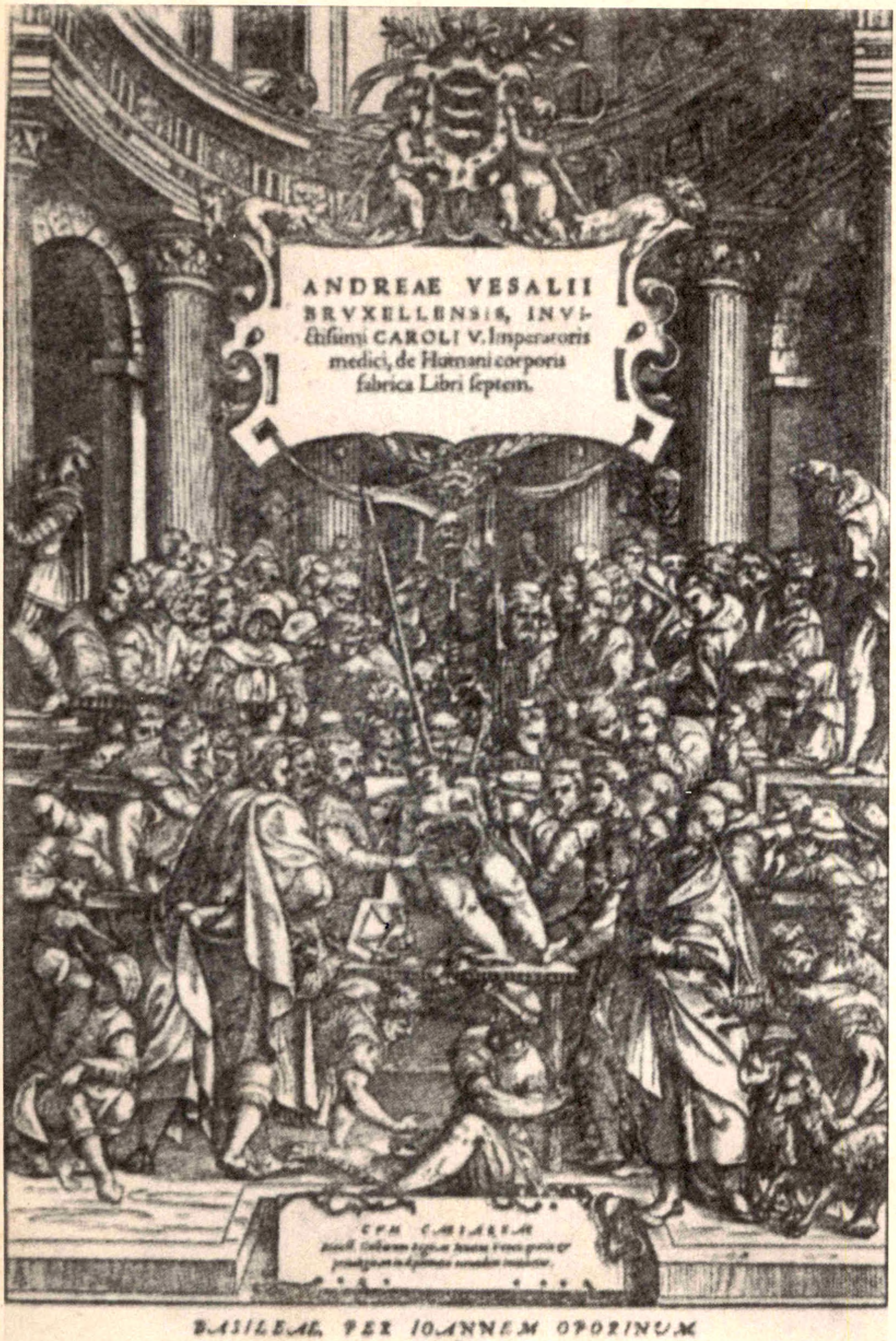
ANDREAE VESALII
BRVXELLENSIS, INVICTISSIMI CAROLI V. Imperatoris
medici, de Humani corporis
fabrica Libri septem.
BASILEAE, PER IOANNEM OPORINUM

FIG. 14. Frontispiece of Vesalius's book *De Humani Corporis Fabrica.* (Courtesy of the National Library of Medicine, Bethesda, MD.)

medicines. . . . You will not find everything written in the books of Galen and Avicenna, all of surgery has not been written, for new times bring new diseases and new books will outmode the old."[103]

Greatest Surgeons of the Renaissance

It was Ambroise Paré (1510–1590),[104] born in Laval, France, himself a barber-surgeon and personal physician

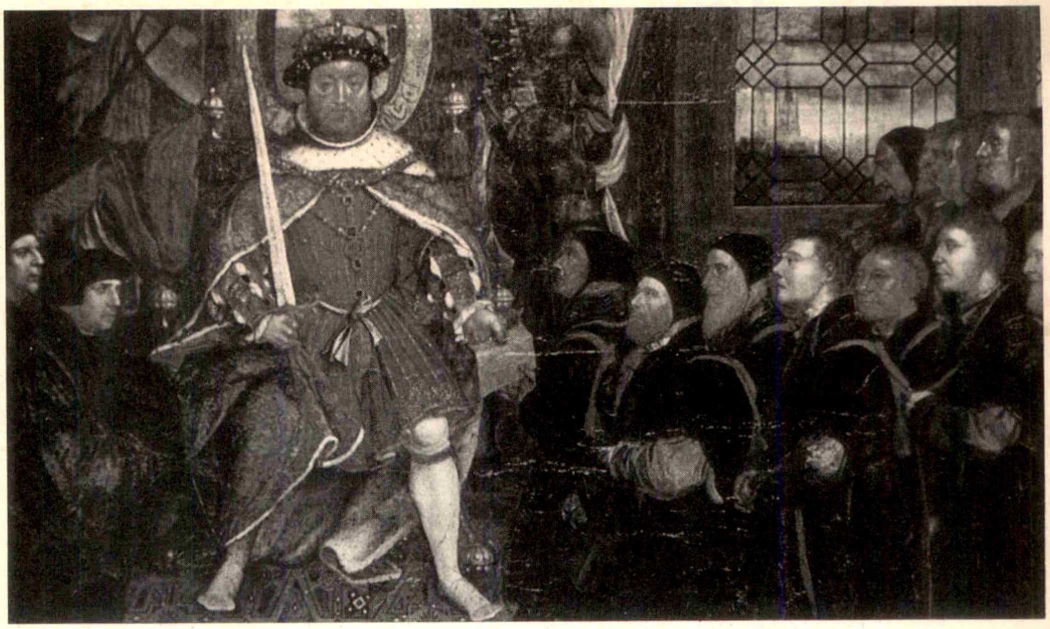

FIG. 15. Hans Holbein's (the Younger) famous painting of Henry VIII in 1540 handing to Thomas Vicary the Act of Union between the Barbers and Surgeons of London. (Reprinted with permission from the President and Council of the Royal College of Surgeons of England.)

to five French kings, who rehabilitated surgery (Fig. 18). A journeyman with a barber-surgeon, Paré attended lessons at Hôtel-Dieu hospital in Paris (Fig. 19), where he participated in dissections. He then became a field surgeon in the army. During that service, he ran out of the boiling oil that was used in treating gunshot wounds and applied instead a healing salve made of eggwhite, rose oil, and turpentine. To his surprise the next morning, those he treated thus showed no inflammation or swelling and little pain, whereas those treated with the burning oil had high fever, great pain, swelling, and inflammation. Thus he resolved never to use burning oil again. His dissertation on gunshot wounds in 1545 became a classic. From their experience and keen observations in military service through the years, consistently surgeons have derived new knowledge from which they have developed new surgical techniques that have benefited not only military personnel but also the civilian population as well.[105]

FIG. 16. Painting of Paracelsus by Jan van Scorel that hangs in the Louvre in Paris. (Courtesy of AS Lyons and RJ Petrucelli,[22] Harry N. Abrams, Inc., New York, NY.)

Paré's second book, primarily about anatomy but containing some obstetrics, was based on his revered Vesalius. His reputation grew, and he became a member of the prestigious College of Saint-Côme, an unusual honor for an unschooled barber-surgeon. His *Anatomie Universelle du Corps Humain* (1561)[19] made Vesalius famous among surgeons. Paré also reintroduced routine ligature of bleeding vessels for wound treatment and amputations (Fig. 20), invented new surgical instruments, designed prostheses for limbs, and improved the hernia band.

At the age of 75 years, Paré published his greatest work, *Oeuvres,*[104] in French; the medical faculty in Paris objected to his breaking the rule that its permission was required for the publication of any medical book, whereupon Paré wrote a denial of the faculty's authority and declared surgery independent of "official whims." His integrity, judgment, surgical skill, and moral stamina elevated him to the height of his profession in his time.

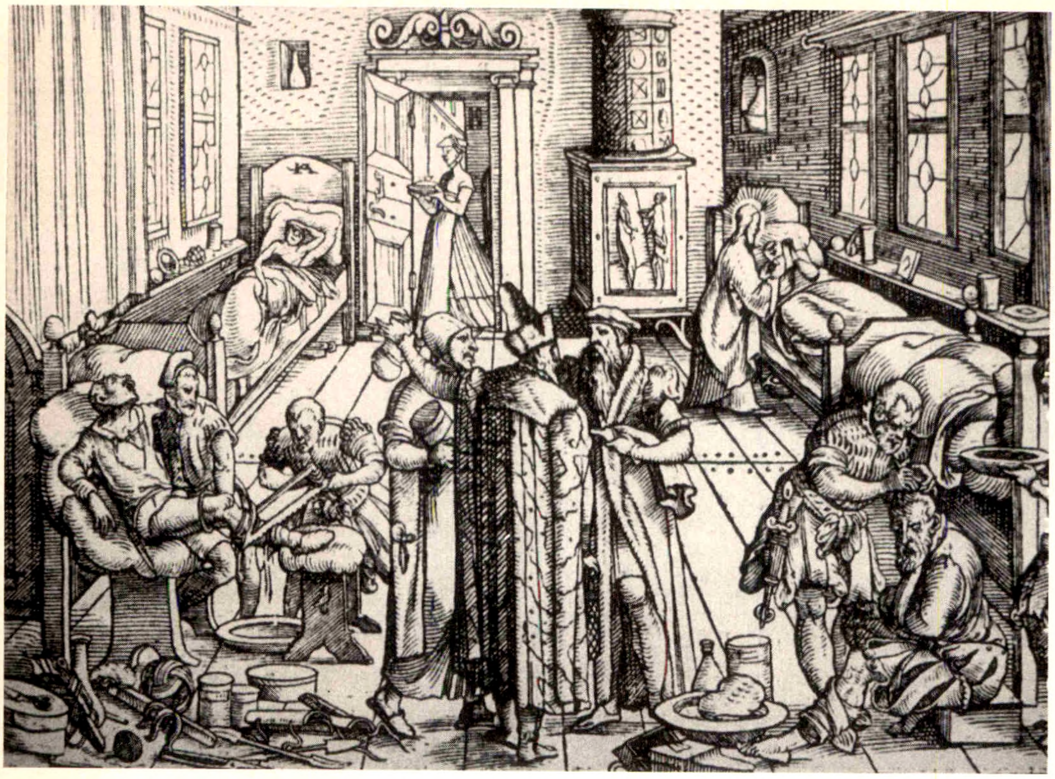

FIG. 17. Woodcut from the title page of Paracelsus's *Opus Chirurgicum* (1565) showing interior of a Renaissance hospital being used increasingly to train physicians. (Courtesy of AS Lyons and RJ Petrucelli,[22] Harry N. Abrams, Inc., New York, NY.)

Specialists of Italy and Germany

In the late medieval period, academic education was at a low ebb, although universities were flourishing in Italy, France, and England. In Germany, where surgeons were definitely in the handicraft tradition, surgery lay dormant; the surgeon, like the carpenter, simply did not study books. Yet the handicrafters were more skilled at caring for wounds than their more learned foreign colleagues, having gained much experience from various wars. The book by Heinrich von Pfolspeundt, *Buch der Bundth-Ertzney,*[106] published in 1460, was notable in

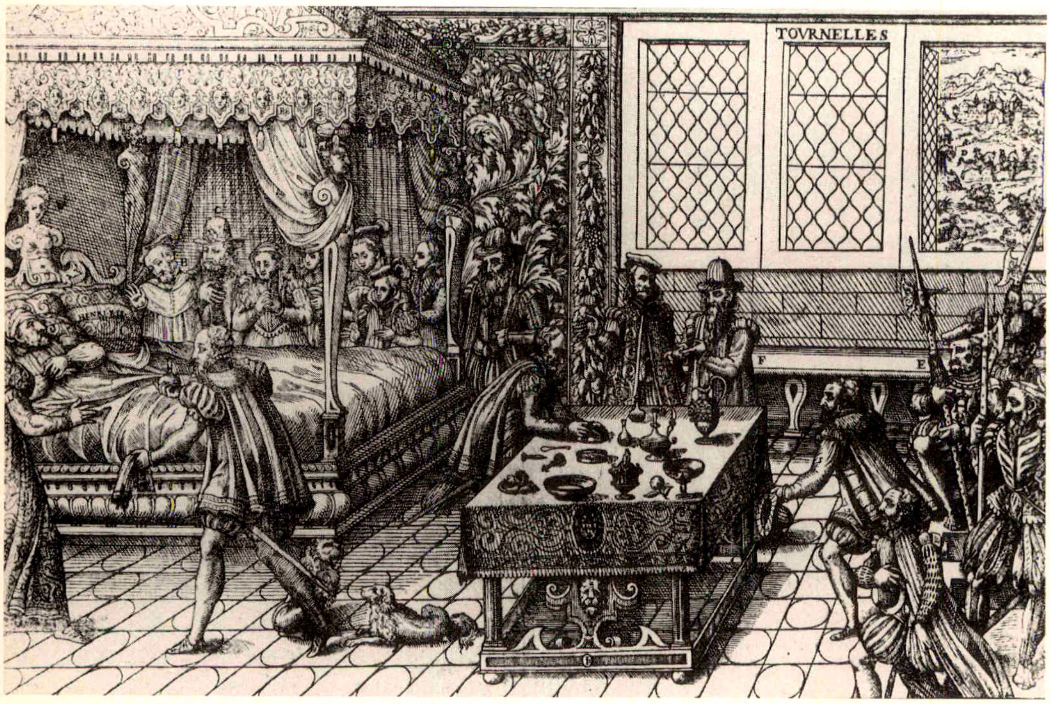

FIG. 18. Woodcut (c. 1560) showing Andreas Vesalius and Ambroise Paré in attendance at the deathbed of Henri II (who had named Paré a master surgeon despite lack of academic credentials). (Courtesy of the National Library of Medicine, Bethesda, MD.)

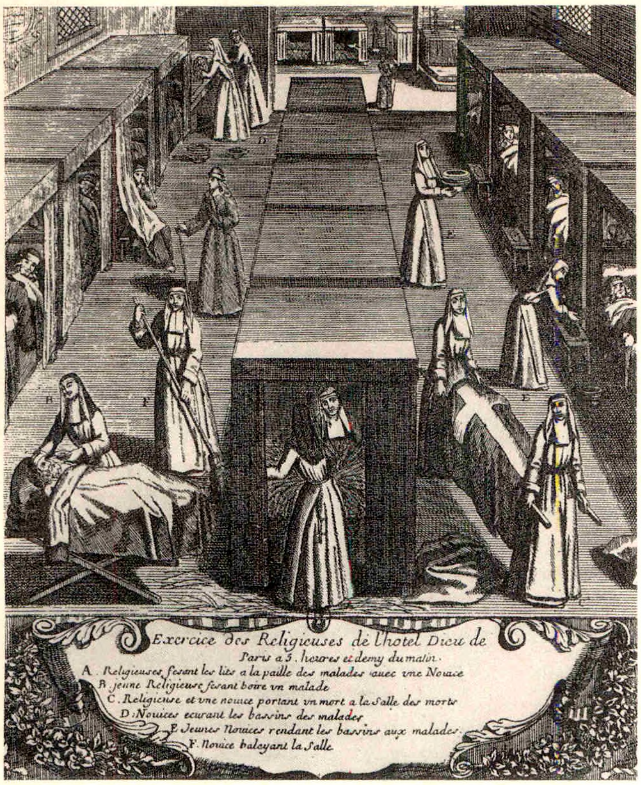
Exercice des Religieuses de l'hotel Dieu de
Paris a 5. heures et demy du matin.
A. Religieuses fesant les lits a la paille des malades avec une Novice
B. jeune Religieuse fesant boire un malade
C. Religieuse et une novice portant un mort a la Salle des morts
D. Novices ecurant les bassins des malades
E. Jeunes Novices rendant les bassins aux malades.
F. Novice baleyant la Salle

FIG. 19. Engraving of interior of Hôtel-Dieu, Paris (c. 1500) revealing crowded conditions and frequency and familiarity of death as corpses are sewn in shrouds in full view of patients. (Courtesy of the National Library of Medicine, Bethesda, MD.)

urging cleanliness; he considered handwashing and clean bandages important.

Medicine as a Science

The descriptions by Andreas Vesalius of the true structure of the human body greatly stimulated medicine and promoted an interest in the functions of the organs, bringing a resurgence of interest in physiology. Vesalius's successor at Padua, Realdus Colombus (1516–1559), who wrote *De Re Anatomica,* taught Michelangelo anatomy.

Heironymous Fabricius ab Aquapendente (1537–1619), a professor of anatomy at Padua, discovered the valves in the veins that permit blood to flow centrally even from parts of the body below the heart.[107] From this discovery, Fabricio's student, William Harvey (1578–1657), was inspired to solve the problem of blood circulation.[18,19]

The New English School

The royal favor shown the Barber-Surgeons' Company elevated its social status, although not on a par with that of the internists. Thomas Vicary began an era of new surgical skills that saw many well-read, inventive, and technically superb surgeons. With his colleague William Clowes (1540–1604), Vicary greatly improved the status of surgery—by supervising the training of apprentices, by teaching, and by watching for untrained charlatans.

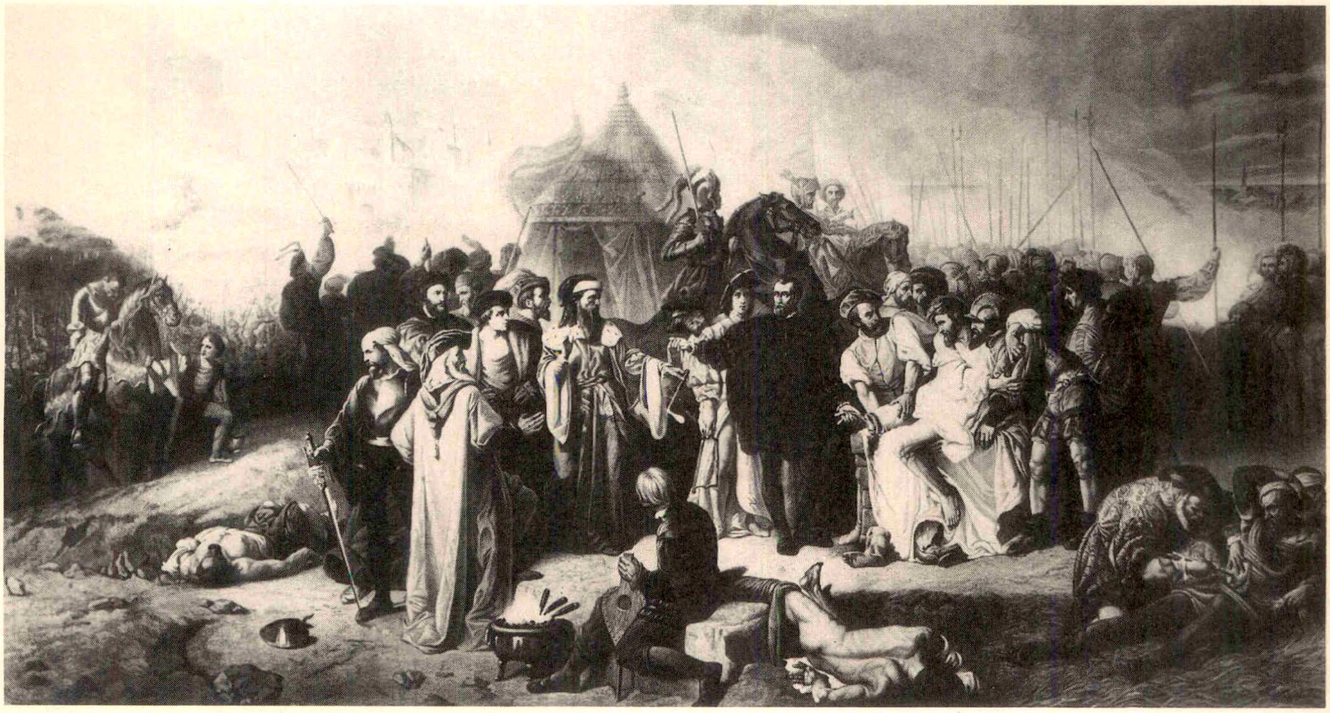

FIG. 20. Portrait of Ambroise Paré applying his ligature during amputation on the battlefield. (Courtesy of the National Library of Medicine, Bethesda, MD.)

Clowes, personal physician to Elizabeth I, was the greatest surgeon in Elizabethan England. His *A Profitable and Necessarie Booke of Observations* was a collection of cases from his own experience.[108] Like Vicary before him and Alexander Read after him, Clowes lectured at the barber-surgeons' guild.

Richard Wiseman (1621–1686) has sometimes been called "the father of English surgery." At the age of 15 years he was an apprentice surgeon and subsequently served his apprenticeship in the Dutch navy. His life was most eventful with extended naval and military service, gaining considerable experience in the handling of the severely wounded. After Charles II became King of England in 1660, Wiseman was appointed Surgeon to the King. Suffering from tuberculosis, he was forced to curtail his activities and turned to writing, analyzing more than 600 personal cases and presenting both his successes and failures, in order "that those that come after me may learn what to avoid." His publication on "Surgical Treatises" not only enriched surgical literature but enhanced the status of surgery.[109,110]

Continental Surgeons

Wilhelm Fabry von Hilden (1560–1634) was the leading German surgeon of his time.[111] With little formal education, he became an apprentice to a succession of barber-surgeons over a period of 12 years. He later became eminently successful in the practice of surgery. He published his experience with more than 600 cases on Observations and Descriptions in Wound Surgery. His careful analysis of this wealth of experience included postmortem examinations to determine the causes of death and the nature of the diseases. He has been regarded as "the best of the surgical empiricists, and not only advanced the surgery of his native country, but also imbued it with the spirit of science."[112]

The Enlightenment

The 18th century in England was a period of vigorous development, not only in statesmanship but also in art, literature, and medicine, built on foundations laid by earlier generations.

William Cheselden, Surgeon

William Cheselden (1688–1752), learned anatomy from another surgeon, William Cowper (1666–1709), who although derided as a "bone-setter," made new discoveries about human anatomy, including Cowper's glands. Competing for corpses, Cheselden ran afoul of the Barber-Surgeons' Society; eventually, he succeeded in separating the surgeons from the barbers with the help of his son-in-law, Dr. Charles Cotes, a member of Parliament and chairman of the special committee of the House of Commons, who brought the matter under consideration, which then resulted in a Bill.[113] He became well known, was officially recognized as personal physician to Queen Caroline, and held three positions as "first lithotomist." Cheselden helped found the new Surgical Society, in 1745, and served as its president until his death in 1752. His significance and influence are best reflected by his disciples and successors, such as Percival Pott, the Hunters, and Astley Cooper, who for almost a century gave British surgery great prestige.[114]

William and John Hunter

Two imposing figures in British surgery were William (1718–1783) and John Hunter (1728–1793) (Fig. 21). William's *Anatomy of the Gravid Uterus*[115] is, according to some, unparalled. It was John Hunter, however, who put surgery on a sound scientific basis and completed the ascendency of surgeons from artisans to scientists. The anatomical drawings that survive reflect his affinity for precision, teaching, and aesthetic sensitivity.

John Hunter was admitted to the Royal Society in 1767; only those with important scientific writings were accepted, and his entrance article was on digestive fluids. He became the city's leading surgeon, inspector of all its hospitals. His writings, published primarily in *Philosophical Transactions,* were later collected into a book.

Hunter's surgical daring is illustrated by an operation he performed for popliteal aneurysm on a patient at St. George's Hospital. Having observed that a rich network of blood vessels developed when the crown of a deer's horn was in its prime and therefore needed nourishment but that the size and number of vessels decreased when the horns shed, Hunter theorized that such reserve (collateral) vessels also developed in human beings when their arteries became obstructed. Thus, the vascular system was not static, but dynamic, subject to supply and demand. When he had a patient with a pulsating aneurysm in his knee-fold who could hardly walk, presumably from an obstruction just below the aneurysm, he rejected amputation in favor of cutting the inner thigh just above the knee (Hunter's channel) and ligating the superficial femoral artery above the aneurysm. The wound formed pus, but this cleared, and the patient left the hospital with his leg intact. Three of four subsequent operations of this kind were successful, the fourth patient, however, having bled to death.[116]

The fact that Hunter never referred to Antyllus,[56] who performed basically the same procedure about 15 centuries previously, or Aetius,[58,59] who also performed a similar procedure about 1000 years earlier, provides written evidence of the discontinuity in the transmission of earlier knowledge and the decline in medical and surgical activities in the Medieval period.

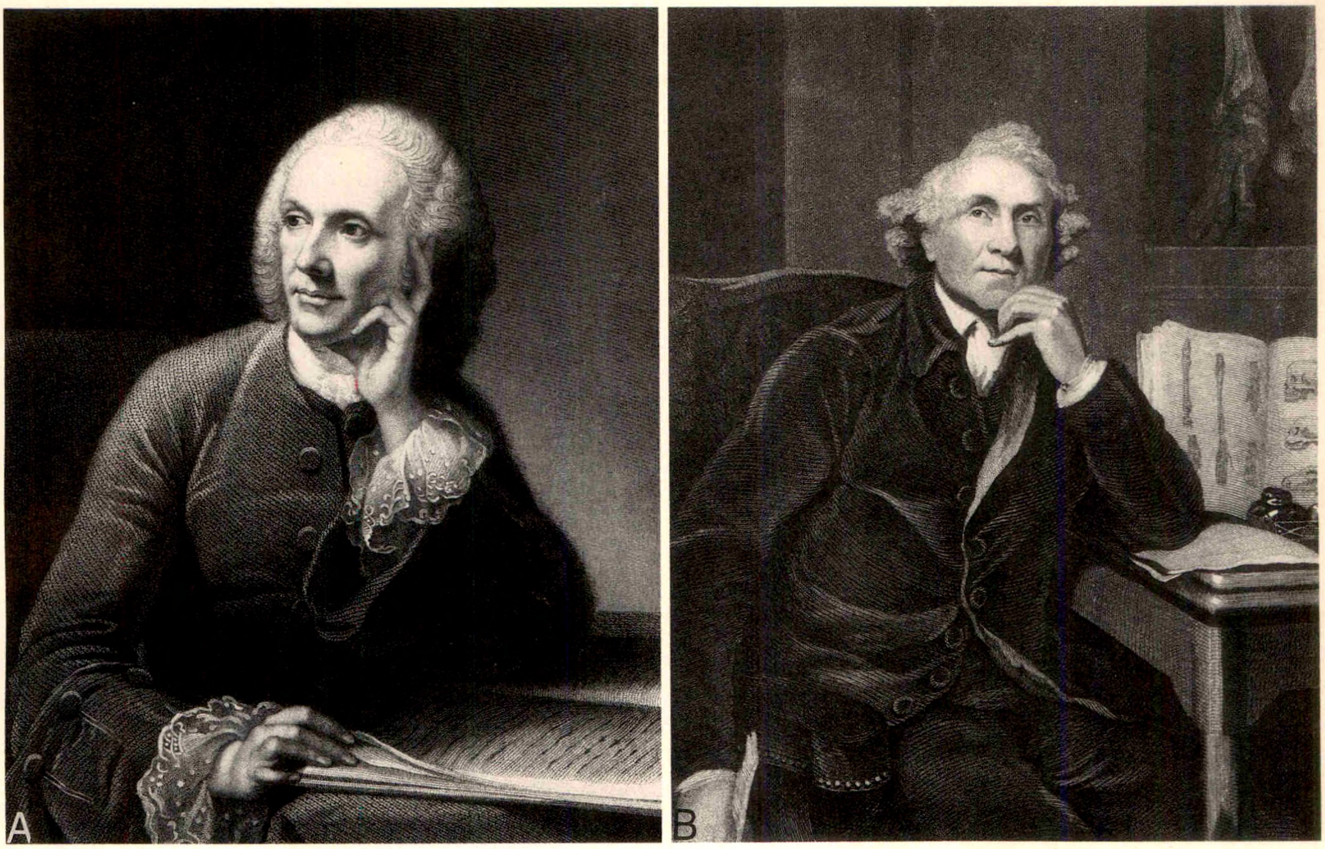

FIG. 21. Portraits of the Hunter brothers, William (A) and John (B). (Courtesy of the National Library of Medicine, Bethesda, MD.)

Hunter developed angina pectoris, and his attacks became increasingly severe and frequent. He did not know the cause of his condition but recorded its manifestations in detail, and he recognized the role of emotional disturbances. He said, in fact, "My life is in the hands of any rascal who chooses to annoy me."[20] That statement was prophetic for in a quarrel with his colleagues at St. George's Hospital regarding teaching programs, he became furious and died within a few minutes. The couch on which he died remains enshrined in the lobby of St. George's Hospital. Long after his death from coronary arteriosclerosis, his admiring disciples succeeded in having his remains moved to Westminster Abbey, where an inscription by the Royal College of Surgeons reads: "to record admiration of his genius, and as a gifted interpreter of the Divine power and wisdom at work in organic life, and its grateful veneration for his services to mankind as the founder of scientific surgery."[117] Some historians have stated that his contributions to surgery have possibly not been surpassed by anyone before or after his time.

Surgeons *Versus* the Academicians

The division between surgeons and "learned doctors" was wider in France than elsewhere, due in part to the pomposity of medical faculties and their resistance to constructive thinking. The surgical competence of the practitioners, however, was not the highest, and, except for Ambroise Paré and some well-known obstetricians, surgery was performed primarily by barber-journeymen. But in 1645 a few surgeons with some literary education merged with the barbers' guild to form a college. The reaction from university physicians was immediate: they forbade the surgeons to bear academic titles and thus prohibited them from calling themselves doctors. Furthermore, the new association was not permitted to call itself a college, which might suggest higher education. Nevertheless, the new organization had money—which the medical faculty lacked—and so built its own demonstration hall for surgical instruction next to the *École de Médicine,* an annoyance to the professors.[10,20] At the inauguration, a fist fight erupted, and the professors were forced to retreat in humble fashion.

Georges Maréchal (1658–1736), personal physician to Louis XIV and Louis XV, established the Académie Royale de Chirurgie.[10,20] It irritated the medical faculty that the monarchy decreed that the Academy would be completely independent and its members would have equivalent ranks and rights as the faculty. Consisting initially of the 70 "master-surgeons" of Paris, the Academy played a major role in rehabilitating French surgery.

Napoleon's Surgeon

When the French Revolution began in 1789, French surgery, including military surgery, was at a low ebb. Hygiene was virtually absent. This was the state when Dominique-Jean Larrey (1766–1842) of Beaudéan began his military career, which covered the entire Napoleonic Age.[20]

In 1792 he became a major with the Rhine army. There he became convinced that better organization was needed to serve the wounded. One idea he had was to save the wounded and dying in the fields by building a cart, which he called "a flying ambulance" and which combined speed with safety and comfort. In 1797, he described his ambulance, including the personnel to accompany it. The ambulance was to be equipped with dressing-barrows, instruments, and bandages. His ambulance became a great success, and he was ordered to return to Paris to arrange ambulances for the entire army.[118]

Four Continental Pioneers

During the 18th century in central Europe, *Surgery,* by Lorenz Heister (1683–1758) of Frankfurt, was the most important influence on surgery, where it appeared in German, English, French, Italian, Dutch, and Latin.[10,20] A well-educated student of languages and the humanities at the University of Hardewyk in Holland, he then went to Amsterdam to study with outstanding surgeons and anatomists. He was appointed chief surgeon of the Army of the Netherlands, where he gained great experience in wound management. After the publication of his book on surgery, he was appointed Professor of Anatomy and Surgery at the University of Helmstadt, where he remained for 38 years. He introduced to Germany a new type of surgeon, one that was highly educated, in contrast to the previously unlettered, craft-trained, and ignorant practitioners.[119,120] Although he advocated simplicity in operations, he improved some surgical instruments and invented some of his own, such as the trepan for removing tonsils. In *Chirurgie* he enhanced surgical standards by his systemization of the subject. The book contained beautiful copper etchings, showing operations step by step. Heister was among the first cancer surgeons and the first to describe appendicitis. "It is necessary," he wrote (1752), "for a surgeon to have complete, or at least very good, knowledge in anatomy as well as in medicine, so that he has enough judgment and understanding to study all the causes and circumstances, and to draw his conclusions from them."[120]

Antonio Scarpa (1752–1832) has been called Italy's sole contributor to surgery at the end of the 18th century.[18,121] His operation for clubfoot is still used in principle today. An able scholar, superb illustrator, brilliant anatomist, and skillful surgeon, he himself illustrated his *Results of Observations and Experience on the Principal Maladies of the Eyes.* Energetic and ambitious, he was despised by some and held in fear by others, but he is memorialized in the many anatomic structures that bear his name. He understood thoroughly the indispensability of a comprehensive knowledge of anatomy and physiology in the practice of surgery. His tireless study bore many fruits, among which were the structure of the eye and inner ear.

In 1804, he compiled a classic monograph on the forms and diagnosis of arterial aneurysms.[122] According to Matas, Scarpa's observations were so convincing that the treatment remained "an immutable and unshaken principle in surgery from the time it was first enunciated by that remarkable surgeon over one hundred years ago to the present time."[121] Not, in fact, until Matas developed his procedure of endoaneurysmorrhaphy, was the "law laid down by Scarpa" successfully challenged. Despite the challenge to Scarpa's surgical interpretations and conclusions, his anatomic and pathologic observations remain unquestioned today.

Balthasar Salinus, a barber-surgeon, was physician to Queen Christina of Sweden and was the first to practice any significant surgery in that country. Because internists were scarce in Sweden, medicine was practiced by barber-surgeons until the 18th century. After apprenticeship in that guild, those who wished undertook theoretical studies at Uppsala or Lund and went abroad for further education.

Olof Acrel (1717–1806), known as the "father of Swedish surgery," learned surgery from an able barber-surgeon, Gerhard Boltenhagen, son of a field surgeon.[21] He traveled to Göttingen to study under Albrecht von Haller, a pioneer in physiology and experimental medicine who also covered surgery. He returned to Sweden and in 1752 established the first general hospital there. Acrel's treatise, *Surgical Events,* a combined handbook and casebook, described operations and instruments in detail and initiated a new native school of surgery. The Acrel Medal is still awarded by the Swedish Surgical Association for outstanding achievement.

Surgery in the Age of Revolutions

The Western World witnessed remarkable innovations during the late 18th and early 19th centuries.

The Great Scots

Surgical education and research at the University of Edinburgh, called the world's medical center in 1800, were started by John Monro (1670–1740) and were continued by his family.[10,18,19] Educated in Leyden along with Herman Boerhaave (1668–1738), he gained much experience as an army surgeon in Holland and Ireland. In 1715, according to his son, he sewed together a patient's severed windpipe and punctured esophagus. His son, Alexander (known as *primus*) (1697–1767), became the first professor of anatomy of the new medical faculty at Edinburgh. The publication of *The Anatomy of the Human Bones* lifted his reputation, and students flocked to him for study. In 1729 a hospital was opened in Edinburgh, later to become the renowned Royal Infirmary. Monro, wrote Oliver Goldsmith (himself a physician), "brought his science to the highest possible perfection."

Monro's son, Alexander *secundus* (1733–1817) carried on his father's work. Educated in London under William Hunter, and in Berlin, where he studied with Johann Friedrich Meckel, Alexander, the son, published *Observations on the Structure and Functions of the Nervous System* (1783), in which he presented the discovery of the connection between the heart's ventricles, called the *foramen Monroi.*

The Bells

The first Scottish surgeon to assemble surgical knowledge into an encyclopedia (*System of Surgery,* 1784),[18] Benjamin Bell was also the first in Britain to advocate radical operation for cancer of the breast according to the technique of Petit in Paris.

John Bell (1763–1820), of a different family, carried on a feud with the dean, who was also a professor of medicine, that caused him to turn against official medicine.[20] Nevertheless, he persuaded his colleagues to question several so-called clinical truths. He showed, for example, that a burst aneurysm could be sewn, and he fought for "primary" healing without pus formation. Perhaps his greatest contribution was his battle for good training in surgical anatomy. He opened his own school of anatomy and earned the title of "the father of surgical anatomy."

After John Hunter

Well trained in anatomy and pathology, and with an elementary knowledge of physiology, the English and Scottish surgeons of the early 19th century were also technically refined. Because physicians were beginning to keep better patient notes and to classify them better than previously, they were learning more from experience and thus improved their diagnoses. With its inspiration from England, surgery of the first three quarters of the 19th century was predominantly British, whereas the last quarter was largely German.

Among John Hunter's first disciples were John Abernethy (1764–1831), whose colorful language added appeal to his special learning.[94] He became a professor of surgery and anatomy at the College of Surgeons and chief surgeon at Saint Bartholomew's. To his students he emphasized anatomy.

Another student of Hunter, Henry Cline (1750–1827), became a surgeon at Saint Thomas' Hospital and was interested in teaching.[94] Still another student of Hunter's was Edward Jenner (1749–1823), who became Hunter's personal assistant but returned home to Berkeley after obtaining his degree to become a country doctor and pursue his hobbies of ornithology and botany. Jenner noted that some people in his home district allowed themselves to be infected by cowpox and that they never caught smallpox, although a rash developed on their hands.

His mentor, Hunter, encouraged him to try an experiment, and on May 14, 1796, he did so by injecting into a young boy cowpox pus from a dairymaid.[94] Six weeks later, when Jenner injected him with smallpox, his slight illness from the first injection made him no worse. The Royal Society rejected Jenner's report of this experiment, and even when Jenner published further evidence of his claim in 1798 in *An Inquiry into the Causes and Effects of the Variolae Vaccinae,* it did not receive immediate acceptance. Although severely criticized at first for his "unethical" experiment, Jenner later became world famous after the appearance of his report of 23 successful vaccinations.

Interestingly, the unlikely early stimulus for experimentation with inoculation was a rigid Congregational cleric, Cotton Mather (1663–1728), who had heard from his African slaves that those who carried the scars of smallpox were the ones who could care for those infected.[123] He persuaded Zabdiel Boylston (1697–1766), a surgeon in Muddy River, Massachusetts, to experiment with inoculation. Because Boylston himself had smallpox scars, he inoculated his son with pus from an active pock, after which his son became mildly ill and recovered. Thereafter, Boylston performed many other inoculations and published his observations in 1726[124] and 1727.[125] Those who had been inoculated were immune when the next epidemic occurred, but inoculation caused some deaths, and Boylston was severely criticized. He was later vindicated, however, and when Edward Jenner's safer method of inoculation was introduced to North America in 1801, this "vaccination" was accepted because of Boylston's success with direct inoculation.

Another leading surgeon among Hunter's disciples was Astley Paston Cooper (1768–1841).[126] As a student at Edinburgh, he was not very scholarly, but then he traveled to London, where he became a surgical aide to Henry Cline at Guy's Hospital (an institution that had been donated by a penitent swindler). He became intrigued by Hunter's lectures and constant experimentation. After successfully removing a large atheroma (cyst) from the head of George IV (with alcohol the only anesthetic), he became Sir Astley Cooper. His greatest contribution, *Treatise on Hernia,* formed the basis for modern hernia surgery.[127] His name remains in *fascia cremasterica Cooperi* and *ligamentum Cooperi,* as well as in the tissue threads holding up the mammary glands.

Cooper's most famous case was in a man admitted to Guy's hospital with abdominal pain.[126] When he found a pulsating tumor inside, he promptly diagnosed an iliac aneurysm, ballooning above and below the left Poupart's ligament. Although no one had ever operated under such circumstances before, Cooper realized that the aneurysm would soon burst and the patient would bleed to death. Indeed, he made the decision to operate after the aneurysm began to bleed. After first testing his procedure on a cadaver in the autopsy room, he operated on the patient, ligating the abdominal aorta just above the bifurcation, and although the patient died 40 hours later, Cooper showed that this kind of operation was possible. It was performed subsequently by several surgeons without success, and in 1923 was successfully completed by Rudolf Matas.[128]

Now pathology entered a new phase in which the basic causes of diseases were being sought. The doctrine of unbalanced body fluids was being abandoned because it did not explain tumors, aneurysms, and many other conditions. Physicians were handicapped, however, in their search for this new knowledge because they were ignorant of the cell, the building block in the human organism.

A detailed publication by Matthias Schleiden (1804–1881) in Germany about how plants are built of cells inspired a friend, Theodor Schwann (1810–1882), to make similar studies of animal tissues.[10] Schwann, who had discovered the enzyme pepsin, confirmed that Schleiden's findings also applied to animals. His observation that nerves are imbedded in an insulating substance—the sheath of "neurilemma" (Schwann's cells)—formed the basis of modern cellular pathology, further developed by Rudolf Virchow (1821–1902).

Virchow's studies led him to microbiology but had little use for bacteriology, an attitude that led him into controversies with other scientists. He did not accept, for example, Koch's epoch-making presentation in 1882 of the causes of tuberculosis.[10] He became a member of Parliament, and his progressive ideas almost led him into a duel with the Iron Chancellor, Bismarck.

Physiology

A number of early physiologists had considerable influence on developments in surgery. Albrecht von Haller (1708–1777), considered to be the founder of experimental physiology, clarified the connection between the nerves and muscles. His eight-volume *Elementa Physiologiae Corporis Humana*[10,18,19] collected all the physiology of his day. Francois Magendie (1783–1855), a professor of medicine in Paris, traced the paths of nerve impulses from the spinal cord and investigated drugs like morphine.[19] One of Magendie's students, Claude Bernard (1813–1878), had a profound influence on surgery (Fig. 22). A shy playwright at first, he was dissuaded by critics from continuing in that field, and he turned to physiology. His major contribution, a view that surgeons did not readily accept, was that, to function normally, an organ required a constant environment. About the inner chemical environment or "homeostasis," Bernard wrote that the free, independent life requires the stability of the internal environment and that the mechanism providing it maintains all the conditions in the internal environment that are necessary for the components' life.[27] His finding of the importance of keeping the body's fluids and electrolytes in proper balance was indispensable to the advancement of surgery. Bernard also studied blood vessels and regulation by vasomotor nerves.

Triumph over Pain

The extraordinary progress made in surgery during the late 19th century can be traced, in considerable measure, to the relief from pain. From antiquity to the Middle Ages, hashish, mandrake, alcohol, and opium were the main analgesics.[129] Many herbs, berries, barks, roots, and flower seeds and blossoms were used to effect loss of consciousness. For the pain of operations, mandragora, poppy, henbane, and hemp were used.

Early literature contains references to various preparations for the relief of pain. In Homer's *Odyssey,*[42] Helen, Zeus's daughter, used a preparation, probably of opium dissolved in wine, to alleviate pain and sleep off grief. In the *Iliad,*[42] Patroclus applied an astringent, anodyne, to relieve pain from Eurypylus's wound. Before operating, the famous Greek physician Dioscorides, in the first century A.D., applied to his patients the root of the mandragora plant boiled in wine. Galen, too, used mandragora to desensitize and paralyze the patient. Mandragora also was used to moderate the agony inflicted on the condemned. Matthew, Mark, and John described the potion that Jesus refused at his crucifixion as gall, myrrh, or hyssop mixed with wine or vinegar. According to Keys,[129] important evidence of Paracelsus as the founder of anesthesia is found in his reference to "sweet vitriol," a distilled mixture of sulphuric acid with alcohol, which was not called ether until it was so named by Frobenius in 1730. Paracelsus had noted that it caused chickens to fall asleep and awaken later without harm, and he therefore recommended "sweet vitriol" as an anodyne that relieves pain. It was Oliver Wendell Holmes who, in a letter of November 21, 1846, to Morton, proposed the terms *anaesthesia* for the state of insensibility produced by ether and *anesthetic* for the agent.[129]

FIG. 22. Painting (1889) by Louis Lhermitte showing the great physiologist Claude Bernard demonstrating an experiment. (Reprinted with permission from the Palais de la Decouverte, Paris, France.)

Heinrich von Pfolspeundt, originally a barber, in his *Bundth-Ertznei* (1460), recommended the use of a soporific sponge as an anesthetic; the sponge was soaked in opium and mandragora and placed over the patient's nose "until he sleeps."[106] Karl Sudhoff had found a recipe for the "soporific sponge" in a ninth-century Monte Cassino *codex,* and Henry Sigerist found such a recipe in Bamberg's ninth-century *Antidotarium.*[10] Possibly an earlier reference to the soporific sponge appeared in the *Antidotarium* of Nicolas of Salerno, believed to have lived in the 12th century.[129] Theodoric reported that Hugo of Lucca prepared a soporific sponge of opium, hemlock, henbane, mandragora, wild ivy, and the seed of a salad plant, which apparently produced anesthesia for surgical procedures. That soporific draughts were accepted before operations is evidenced by various literary references, including that related by Dioneo in Boccaccio's *Decameron* (14th century),[130] in which a patient drank a potion that caused him to sleep for whatever interval was necessary to complete the operation.

In the United States in the early 19th century, use of ether and nitrous oxide was progressing. Interestingly the use of these gases in anesthesia was promoted by their inhalation for pleasure at "laughing-gas parties." A young chemistry student, William E. Clarke, a participant in these sessions, used ether anesthesia in what was considered to be its first recorded use, for a tooth extraction in January 1842, in Rochester, New York.[129] On March 30, 1842, in Georgia, Crawford W. Long, who had witnessed "ether frolics" at the University of Pennsylvania, used ether as an anesthetic before removing a small tumor from his patient, James M. Venable. He did not, however, publicize this event, and it was not until December 1849 that he described this experience in the *Southern Medical and Surgical Journal.*[131]

Three years earlier, in the *Boston Medical and Surgical Journal,* Bigelow and Warren had reported the work of dentist William Thomas Green Morton (1819–1868), who had pursued the matter of anesthetization.[132] After much experimentation and following the suggestion of one of his teachers, Dr. Charles A. Jackson, to use pure sulphuric ether, Dr. Morton successfully performed a tooth extraction after inducing his patient to inhale the ether. Morton next asked Dr. John C. Warren to try the anesthetic during some operation, and that was done on October 16, 1846, when the patient, Gilbert Abbott, inhaled the vapor from Morton's new anesthesia apparatus, before Dr. Warren removed a tumor from the patient's jaw (Fig. 23). Whereas Warren considered it an obligation to introduce to other surgeons and hospitals this valuable innovation, Morton wished to keep the matter a secret and to obtain an exclusive patent for its use. Warren decided that, without a full knowledge of the apparatus and the agent, he could not ethically publicize its use, a position that prompted Morton not to keep his method a secret.[133]

Surgery in the United States

Surgery in this country has played a highly significant role in the advancement of medical knowledge, training, and research, particularly since the turn of this century. Since the history of surgery in the United States has been

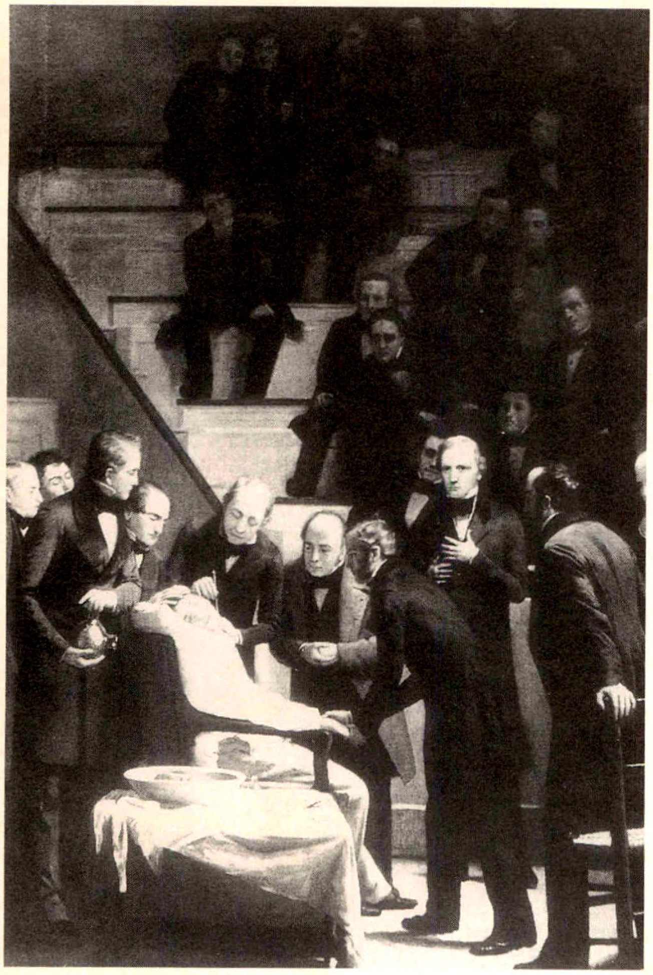

FIG. 23. The famous painting (1882) by Robert Hinckley of the first successful public demonstration of surgical anesthesia (October 16, 1846) using ether at the Massachusetts General Hospital in Boston, Massachusetts. (Reprinted with permission from the Boston Medical Library in The Francis A. Countway Library of Medicine, Boston, MA.)

well recounted by a number of others,[123,134–137] it is neither necessary nor appropriate to detail this development here. Moreover, one of our former Presidents, David C. Sabiston, Jr., in his Presidential address before this body 16 years ago, presented a fascinating account, in his usual scholastic manner, of the major contributions to surgery from the South.[138]

In accordance with this perspective of surgery, however, there are certain characteristics, qualities, and observations concerning the development of our specialty in this country that deserve consideration for several reasons. For one thing, this period of surgical development took place within a relatively brief interval, less than a century, and with accelerating rapidity. For another, it has largely, if not uniquely, been achieved by American surgeons.

To be sure, much of the underlying basis for some of these developments was begun in Europe, especially in the earlier period. These include antisepsis and asepsis following Lord Lister's doctrine; establishment of medical school faculties and university teaching hospitals, originally developed by physicians and surgeons who obtained their training in Europe, with the establishment of specialized disciplines both in basic medical science and clinical activities; and great expansion of animal research laboratories in surgery.

One of the most important developments in surgery that is uniquely American in concept and implementation is the residency training program that was initiated by Halsted at Johns Hopkins Hospital.[139] To some extent, this was based on his observations of the methods of training surgeons in Austria and Germany, where surgery had been greatly advanced. He noted, however, that because the Oberartz, or Chief Resident, often remained in this position until he was chosen to head a Department of Surgery, sometimes as long as 10 years, only a few surgeons could be trained. Accordingly, he modified the program to provide for the Chief Resident to serve for only 2 to 3 years. So successful was this concept that it was ultimately standardized for the nation. Along with this development, and to a large extent stimulated by its success, there were established national qualifying boards and committees for accrediting the residency training programs and for certifying surgeons who had completed such training. It is not insignificant that none of these developments was initiated or supported by the government.

The rapid progress or ascent of surgery, as so eloquently expressed by the Wangensteens in the title of their book, *The Rise of Surgery,*[140] that has taken place in the latter part of the last century, and especially in the past four or five decades, was initiated by two important discoveries, one of European origin and the other of American origin. The former was the doctrine of antisepsis and asepsis, first propounded by Semmelweis (1847)[141] and Lister (1865),[142,143] based on the works of Pasteur[144] and Koch,[145] and the latter was general anesthesia with ether by Crawford Long of Georgia (1842) and William Thomas Green Morton (1846) of Massachusetts.

With these developments, surgery was significantly altered from its century-old status of an emergency high-risk character to a more deliberate elective nature. It now became possible for surgeons to pursue technical innovations for the treatment of a wide variety of lesions and diseases and to develop more meticulous surgical techniques with greatest regard for tissue in wound management and repairs. Accordingly, surgery gained greater respect both in the medical and lay communities.

Another important contribution of American surgery was the development of thoracic surgery, largely as a consequence of tracheal insufflation, first used by Matas[146,147] and subsequently simplified and perfected by Samuel Meltzer and John Auer.[148] This development obviated the cumbersome efforts of Sauerbruch (1904) to use a negative pressure cabinet for thoracic operations. Its great significance may be better appreciated when it is realized that it was the key that opened the door to surgical methods of treatment of mediastinal tumors, bronchiectasis, and other diseases of the lung, including particularly cancer and congenital and acquired cardiovascular diseases with open-heart surgery.

Perhaps no other branch of medicine has enjoyed the striking advances that have occurred in surgery, not only technically but also from the conceptual and cognitive points of view, and indeed in the objectives.[149] Before the turn of this century, indeed, as already indicated, the objective was largely extirpation of the diseased tissue or organ and urgent care of the wounded, with reconstruction of the tissue, whereas surgery has since focused on preservation or restoration of function, as well as cure of the underlying disease. As so well expressed by the Wangensteens in the subtitle of their book, *The Rise of Surgery,* surgery advanced "From Empiric Craft to Scientific Discipline."[140]

Surgery has also branched into a number of subspecialties. Although ophthalmology had begun to develop much earlier, most of the other surgical subspecialties, such as urology, obstetrics, and gynecology, began being organized shortly before the turn of the century. Neurosurgery, orthopedics, and plastic surgery followed, stimulated by developments during and after World Wars I and II.

Contributing to the exciting surgical advances, the rise of ancillary services included:

(1) induction of anesthesia, which, although as indicated previously, was introduced about the mid-19th century by Long and Morton, has since been refined both pharmacologically and technically, including the mechanical ventilation of the lungs;

(2) chemotherapy, particularly the use of antibiotics for the control of infection;

(3) blood transfusion, with the discovery of four blood groups by Landsteiner and Moss and the introduction of citrate as an anticoagulant, which made the procedure safe and readily available through blood banks, along with individual blood components for specific deficiencies;

(4) more precise diagnostic methods and procedures, including x-ray (following its discovery by Roentgen in 1895), along with angiography with use of radiopaque substances to visualize circulatory diseases and various cardiovascular organ functions and abnormalities, and more recently computed axial tomography (CAT) scan, positron emission tomography (PET), ultrasound, and magnetic resonance imaging (MRI);

(5) intermittent or continuous monitoring of various vital signs, gases, and cardiovascular functions; and

(6) heparin as an effective anticoagulant to prevent thrombus formation and to permit maintenance of prolonged circulation with the heart–lung machine.

The Impact of Socioeconomic Forces

The unprecedented and unforeseen changes in medicine since the turn of the century, while greatly extending our longevity and the quality of life, have also seriously complicated the delivery of health services, have altered the traditional physician–patient relationship, and have created thorny problems for patients, physicians, and the public.[150] Prominent themes during the past several decades have included cost-benefit analysis, cost containment, HMOs, PRSOs, health-care accessibility, national health programs, alternate delivery systems, Medicare payments, malpractice insurance, voluntary accreditation, quality assurance, medical ethics (including the controversial active euthanasia and fetal tissue research), scientific misconduct, and an accelerating, indeed alarming increase in governmental regulations. In the words of Eli Ginzberg, ". . . the earlier untrammeled freedom of the profession to determine how, where, and for how long patients would be treated is being circumscribed by new rules, regulations, and protocols."[151]

The vigorous campaign waged by animalists against medical research, involving sensationalism, false information, terrorism, and intimidation, has adversely influenced some segments of society and has swayed some members of Congress.[152] These actions have cost research institutions millions of dollars, have curtailed or completely halted some valuable research programs, and have discouraged some promising young candidates from entering research. The total effect on medical research, which is the source of new medical knowledge, has been devastating.

Physicians are becoming increasingly disenchanted, many are leaving the profession, and fewer of the best and brightest are applying to medical school. The source of their displeasure? Medical practice no longer brings a sense of satisfaction; it is simply not worth the personal frustration and financial investment. Physicians are no longer permitted to decide how to take care of their patients on the basis of their medical knowledge and training. Now third-party payers, the government, and various and sundry committees of self-designated "experts" dictate hospital admission policies, diagnostic studies, type of treatment, and length of hospital stay. Many of these so-called "experts" have never even studied medicine or practiced a day in their lives, and some who have are unfamiliar with the nuances of a particular case.

In this connection, Sir Raymond Hoffenberg, while President of the Royal College of Physicians, published in 1986 the Rock Carling Lectureship entitled *Clinical Freedom,*[153] in which he analyzed the "winds of change" in medicine both in Great Britain, where a state medical service was established more than four decades ago, and in the United States, and stated that "on balance, despite our recruitment to a State-run service, we have retained a substantial degree of clinical autonomy, perhaps—one might venture—somewhat more than our colleagues in America who are less overtly subject to government control."[153] He stated further that "a 'decline in clinical freedom' has taken place, and is still taking place, to a greater extent in their commercialized and competitive system than in our nationalized, bureaucratic, and more tightly controlled NHS."[153] To support this belief, he quoted Dr. George Silver as follows: ". . . the British doctor, discontented as he or she may be with the inadequacy of the financial rewards of practice in the UK, or dissatisfied with the shabby and inadequate facilities in many places in which medical work is performed, is still largely free and untrammelled in the practice of medicine, . . . (whereas) American physicians . . . are pinioned by regulations and controls far beyond . . . colleagues in most other countries."[154]

The cost of a medical education in time and money is considerable, and the expense of starting a medical practice and of malpractice insurance is exorbitant. The increasing litigiousness of our society has exerted additional pressure on physicians, many of whom believe that they must practice defensive medicine. Yet they also feel they are in a no-win situation: If they order certain tests as a defense against a malpractice suit, they will be accused of increasing the patient's costs unnecessarily; if they do not order the tests, they will be accused of being negligent or incompetent. The general decline in esteem of the profession also contributes to the exodus from medicine. If this trend continues, the efforts of those who profess to "reform" the profession will be self-defeating, because the quality of health care and its accessibility, which the so-called reformists are clamoring to solve, assuredly will decline notably.

The extraordinary progress made in medicine during the past century is in serious jeopardy today.[155] The intrusion of extramedical elements also has disturbed the physician–patient relationship, which is so crucial to effective health care. Despite the remarkable wonders of modern medicine, the patient remains the center of medical practice, and the physician–patient relationship is still the most critical element in effective health delivery. Anything that interferes with that is a self-defeating obstacle. One of the most important challenges of the future, therefore, is to restore the confidence of the public in the integrity and dedication of the medical profession and to revive the trust of individual patients in their physicians.

A troubling trend is the decline in support for medical research during the past decade or so. A negative impact of the cost-containment hysteria associated with reduction of the budget deficit is the creation of an unstable environment within the research community. The loss of promising young medical science investigators is particularly critical because the continued integrity of the nation's medical research enterprise depends largely on the availability of a pool of talented researchers, and that pool is now being depleted.

All of the wondrous medical advances that have been so briefly touched on in this presentation rest on research. It would seem unnecessary to emphasize its seminal need and its adequate support, as well as its strong protection against a minority of zealous, aggressive, and often irrational groups dedicated to its elimination. Research remains our most important and, indeed, our only means of solving the remaining problems in medicine and thus of further improving the health of the people. Indeed, the valuable advances presented here clearly establish the validity of that concept.

Cost Containment

As surgical research yielded greater and more dramatic advances, such as open-heart surgery, transplantation, and mechanical cardiac assistors, it became costlier. These "medical miracles" excited the public, who began demanding their benefits, but balked at paying for them. Other fruits of technologic development, such as imaging, met with similar public reaction. The rising cost led the government to underwrite part of the health-care program, and as critics and the press focused increasingly on accelerated costs, medical practice became the subject of inquiry. The government intruded, presumably to control costs, but its methods proved not only ineffective, but cumbersome and obstructive. The resulting constraints limited the extension and quality of surgery, for the surgeon's quest is no longer determined by the intellectual capabilities of surgeons, but by external factors—government and quality-assurance criteria. Despite these constraints, however, the quality of surgery has remained high.

Cognitive and Noncognitive Medicine

It became popular in recent years to divide medicine into cognitive and noncognitive disciplines—a throwback to the schism between medicine and surgery in the Dark Ages, when use of the hands was demeaned and the status of surgery, and indeed of all medicine, declined significantly. But the labeling of surgery as a noncognitive discipline is fallacious and totally unsupported by its history and achievements. To suggest that surgeons are merely noncerebrating technicians is to ignore their native intelligence, education, rigorous training, and performance. The history of surgery is replete with scholarship, and with innovative and highly creative activities, all highly cognitive endeavors, as well as with invention of instruments and new operative techniques and procedures. Any surgeon worth his salt arrives at a judgment regarding operative treatment on the basis of his own knowledge of the basic sciences and clinical medicine. Indeed, the training of a surgeon is equally as intense and is usually longer than that in other disciplines. Such an investment, with its personal and financial sacrifices, was apparently ignored by the advocates of the RBRVS formula.

Moreover, every development in surgery is based on cognitive phenomena and is preceded by careful reasoning and carefully designed investigations. Consider the surgical treatment of congenital cardiac malformations, aneurysms, stroke, coronary artery disease, and organ transplantation. Were these and other life-saving operations developed by those in so-called cognitive disciplines—or by practicing surgeons?

One of the most highly publicized reports regarding the new terminology and criteria for payment originated at Harvard, where, owing to its widely held perceptions as a scholarly institution, one would not expect vogue words to be used loosely and imprecisely.[156,157] The play that the sensational results of this study received in the public press led to calls for "restructuring" of medical fees according to a "resource-based relative-value (RBRV) scale," that is, measurement of "relative levels of resource input expended when physicians produce services and procedures," which is "a function of the physician's work input, the opportunity cost of specialty training, and the relative practice costs for each specialty."[157] The language is hopelessly vague and jargonish. Hsaio and coauthors[157] concluded that "Invasive procedures are typically compensated at more than double the rate of evaluation-and-management services, when both consume the same resource inputs" and that "the average family practitioner could receive 60 percent more revenue from Medicare," whereas "the average ophthalmologist and thoracic and cardiovascular surgeon could receive 40 to 50 percent less in revenues from Medicare."

The formula used to obtain their results "assumed work input to consist of time; *mental effort;* knowledge, and judgment, and diagnostic acumen; technical skill; physical effort; and psychological stress."[156] The idea of quantitating many of these qualitative factors is mind boggling, but it was apparently attempted with impunity. The authors concede that mental effort, technical skill, and stress are virtually impossible to measure objectively, so they blithely relied on "subjective judgments of the physicians who perform particular procedures." Interestingly, of the six authors of the Special Report, only one was a medical doctor (not a practicing surgeon) and was therefore familiar with what is involved in the daily work of a physician. The final statement in the article by Hsaio and coworkers[156] was almost a self-fulfilling prophecy: "This study indicates that resource-based relative values could serve as a rational foundation for compensating physicians according to the work and effort they exert in performing services."

Had the Harvard group that divided medical practice into "cognitive" and "noncognitive" been too lazy to consult a dictionary or had they been unable to understand the lexical entries, they could have consulted the University's English Department for an explanation of the correct definitions of these terms. "Cognitive" is from the Latin *cognitivus*, meaning "of or pertaining to knowledge." By that definition, if surgery is a *non*cognitive discipline, surgeons have no knowledge—presumably only technical skills. In earlier times, when barber-surgeons were unlettered, perhaps the term may have been applicable, but certainly not today. Because of the patent absurdity of this artificial division on the basis of intellectual involvement, because of the weakness of the arguments, and because of the failure to substantiate the arguments with valid evidence, the dichotomy of "cognitive" and "noncognitive" has now been dropped, only to be supplanted by the equally unacceptable and imprecise "procedural" and "nonprocedural." But some damage was unfairly done to the image of surgery and surgeons.

The folly and fallacy of the new terminology and criteria proposed largely by nonpractitioners and adopted by bureaucrats to gauge the monetary value of various kinds of health services deserves exposure. So do the inanity of the new lexicon and the infirmity of the thinking that underlies it. This is the same kind of mentality that introduced such dehumanizing terms as "consumer" for "patient" and "provider" for "physician."[158] "No factor has tarnished the public perception of the profession more than its flagrant commercialisation," wrote Sir Raymond Hoffenberg. "In a society in which doctors are seen as 'providers' of marketable health-care products to 'consumers' or 'clients,' their standing in the community is assumed to warrant no more recognition or respect than that of other purveyors of essential goods."[153] This public perception has been enhanced by the importunate hawking of medicine and solicitation of patients on television and in other news media as though they were, indeed, advertising a "product."

The volume of "reforms" proposed by self-named health-care experts is exceeded only by their almost universal inexperience in the actual practice of medicine. If surgery were a purely technical skill, requiring no knowledge of the basic and clinical sciences, it would hardly take 10 or more years for licensure and certification. How many surgeons do you know who, when the patient is on the operating table and an unexpected finding occurs, call in a "cognitive" practitioner to advise him how to proceed? The new nomenclature is only the most recent manifestation of the attempt to devalue and demean surgery, ostensibly in the interest of cost containment.

The foregoing surgical perspective attests to the impressive, durable contributions of surgeons throughout medical recorded history. But it also documents their periodic censure and denigration as noncerebral, insensitive, avaricious, and even venal technicians. In the Babylonian, Indian, Egyptian, and Classical Greek eras, surgeons were esteemed as educated professionals, but during the Roman and later Medieval periods, physicians were discouraged from using their hands in caring for patients by sacrodotal and other factors previously described. The consequence was a separation of medicine from surgery. This arbitrary division has recurred in various forms ever since, to the detriment of both branches of medicine. As T. Clifford Allbutt[45] has so aptly stated: "From Greece and medieval Italy we have to bring home the lesson that our division of Medicine into medicine and surgery had its root not in nature, nor even in natural artifice, but in clerical feudal and humanistic conceits." Interestingly, when these efforts at estrangement have succeeded, the status of medicine in general has declined, whereas when the two branches worked together harmoniously, the entire profession flourished, made remarkable progress, and thus served humanity better.

It deserves emphasizing that in every period of history, surgeons of keen intellect and high purpose, by observing and recording their astute clinical and experimental observations, have helped build the estimable body of medical as well as surgical knowledge available today. Reaching beyond the manual procedure of operating, they have probed the anatomy, physiology, and biochemistry of the human body and the changes that occur as a consequence of disease or injury, to develop better methods of diagnosis, treatment, and prevention. Despite the impediments imposed on early surgeons, giants like Paracelsus, Paré, and Hunter, all barber-surgeons, refused to succumb and instead engaged their inquiring minds in investigations that uncovered important concepts. The results of their inquiries not only improved surgery but also enriched all of medicine. Thus, tradition testifies to the fact that regardless of the barriers or the resistance, surgery will prevail in time. The reason is clear: surgeons have always made practical contributions, and in time society not only appreciates those services but also demands them.

To the criticism, and sometimes even the humiliation, directed to them, surgeons have responded in a constructive way by trying to improve the education, performance, and ethics of their colleagues. Thus, they have erected exacting training requirements, licensing and certification regulations, and high ethical precepts for their profession. These measures have lifted surgery from its status as the craft that some, in earlier times, and a few with dangerously powerful influence are now trying to assign it, to its current position as a respected healing science.

Today we are faced with new impositions inimical to the optimal delivery of our services—factors that threaten to erode the future of surgery. The ever-mounting government restrictions and intrusion into every decision regarding patient care; the anti-intellectual and antiscience attitude, characterized by the antagonism of groups like the animal rights zealots; the menace of malpractice litigation; and the consistent diminution in funding for research—all have a deleterious effect on our profession by diverting our attention from our primary concern—our patients. Some hospitals today spend as much as $2 million each year on quality assurance activities imposed on them, without observing any improvement occurring in patient health care.

In the face of these and other hostile forces, however, I continue to be optimistic about the future of surgery, and that optimism is reinforced by my recollection of the dauntless spirit of our predecessors—their unquenchable curiosity, their dogged determination, their indomitable courage in opening audacious new frontiers, their basic meliorism, and their innate desire to alleviate human suffering. I see all these qualities in my colleagues gathered here today, and I feel a surge of great pride in being a member of such an honorable, dedicated, and productive group. You have added luster to the mantle of surgery and will, I know, pass on to the next generation of surgeons the intrepid spirit that has always distinguished our profession. Thank you, and may the future bring you only the best that life has to offer.

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SCIENTIFIC PAPERS

Pelvic Fracture from Major Blunt Trauma

Outcome Is Determined by Associated Injuries

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Pelvic hemorrhage has been implicated as the cause of death in 50% of patients who die following pelvic fractures. To establish correlates of morbidity and mortality from pelvic fractures due to blunt trauma, we reviewed 236 patients treated during 4 years. The average age of the 144 men and 92 women was 31.5 years, the average Injury Severity Score was 21.3, the average blood requirement was 5 units, and the average hospital stay was 16.8 days. One hundred fifty-two patients (64.4%) were injured in motor vehicle accidents, 33 (14%) had motor vehicle-pedestrian accidents, 16 (6.8%) had crush injuries, 12 (5.1%) each had either motorcycle accidents or falls, and 11 (4.6%) had miscellaneous accidents. Eighteen patients (7.6%) died, with seven (38.9%) deaths due to hemorrhage. Only one death was caused by pelvic hemorrhage. Other deaths were due to hemorrhage from other sites (6), head injury (5), sepsis or multiple-organ failure (4), pulmonary injury (1), and pulmonary embolus (1). None of the septic deaths was related to a pelvic hematoma. Multivariate multiple regression analysis showed that the severity of injury was correlated with indices of severity of pelvic fractures such as fracture site ($p < 0.0001$), fracture displacement ($p < 0.005$), pelvic stability ($p < 0.0001$), and vector of injury ($p < 0.01$). However death could not be predicted on the basis of these indices of severity ($p > 0.28$). Of the nine patients who underwent pelvic arteriography, three required embolization of actively bleeding pelvic vessels, but seven had intra-abdominal hemorrhage that required laparotomy, and eight developed a coagulopathy. Massive bleeding from pelvic fractures was uncommon, and the major threat of hemorrhage was from nonpelvic sites. Furthermore, although injury severity was correlated with the severity of the pelvic fracture, hospital outcome was determined by associated injuries and not by the pelvic fracture.

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THE PELVIS POSSESSES exceptional inherent strength and major external forces are required to fracture the normal pelvis. The large volume of highly vascular cancellous bone and the anatomic proximity of major blood vessels makes severe hemorrhage the most dreaded immediate complication of pelvic fractures. Recent reports incriminated hemorrhage as the cause of death in about one half of patients who died following pelvic fractures.[1,2]

The considerable forces necessary to fracture the pelvis are often delivered to other areas of the body. Associated injuries are therefore common, and these injuries may contribute significantly to the outcome of patients with pelvic fracture. Because in our experience exsanguination from the pelvis was an uncommon event, we tried to determine the correlates of morbidity and mortality in our patients with pelvic fracture. This was accomplished through a 4-year retrospective review of our experience with this clinical problem.

Materials and Methods

The medical records of all patients admitted to the University of Mississippi Medical Center (UMC) from January 1986 through December 1989 with a diagnosis of pelvic fracture were reviewed. Only those patients with pelvic fracture from blunt trauma who were initially admitted to our hospital were included in the study. Patients who were evaluated and stabilized in another hospital before transfer to our facility were included, but those who were admitted to another hospital, underwent more extensive treatment, and were later transferred to UMC were excluded. Also excluded were patients with penetrating wounds to the bony pelvis, those with pathologic fractures of the pelvis, and patients with avulsion fractures or fractures of only the acetabular rim.

In addition to demographic information and mechanism of injury, a number of criteria that reflected the se-

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verity of injury were recorded for each patient. These criteria included systolic blood pressure, respiratory rate, and Glasgow Coma Score in the emergency room; revised Trauma Score; volume of asanguinous resuscitation fluids received in the emergency room; blood transfusions received during the first 48 hours; duration of hospital stay; number of days in the intensive care unit; cause of death, if applicable; total hospital charges; associated injuries and Abbreviated Injury Scale (AIS) scores for each anatomic system;[3] and Injury Severity Score (ISS) calculated by the method of Baker et al.[4] The site to which the patient was discharged was recorded as home, other (rehabilitation facility, other hospital, or nursing home), or death.

Pelvic roentgenograms were reviewed on all patients. In addition to standard anterior–posterior views, inlet and outlet views of the pelvis were obtained in all but a few patients. In most instances computed tomography of the pelvis was performed as well. The vector of pelvic injury was determined from a consideration of the fracture pattern as well as from the mechanism of injury. The major vector of injury was classified into one of the following categories as defined by Pennal et al.,[5] and Young et al.[6]: anterior–posterior compression; lateral compression; and vertical shear. When there appeared to be at least two vectors of injury, the fracture was classified as caused by ‘multiple forces.’ Impaction injuries were defined as fractures in which the femoral head was impacted into the acetabulum without any involvement of the rest of the pelvis. When the vector of injury could not be determined it was listed as ‘unknown.’ Most of the latter were isolated pubic or ischial ramus fractures. Each pelvic fracture also was classified as open or closed. An open fracture was defined as one in which the skin overlying the fracture was violated, or in which there was an injury to the rectum or vagina. Fractures associated with injuries to the urinary bladder or urethra were considered to be closed. The anatomic segment of the pelvis that was involved by the fracture was recorded. These categories were acetabulum, ilium, ischium, pubis, sacrum, or multiple sites. The maximal displacement of the fracture fragments or the gap between separated elements of the pelvis was measured and categorized as none, mild (less than 1 cm), moderate (1 to 2 cm), or severe (more than 2 cm). Finally each fracture was classified as either stable or unstable. An unstable fracture was defined as one in which the pelvic ring would not be stable with weight bearing because of involvement of the anterior elements (pubis and or ischium) as well as loss of integrity of the posterior elements, either osseous or ligamentous.

During the period of review, the standard management of patients with pelvic fracture at UMC was resuscitation with lactated Ringer's solution and blood if needed. All patients had roentgenograms of the cervical spine, chest, and pelvis. Additional films of the spine, extremities, and urinary system were obtained if clinically indicated. Patients with obvious or suspected head injuries underwent computed tomography. In addition to clinical examination, the abdomen was evaluated by diagnostic peritoneal lavage by a supraumbilical approach, or by computed tomography if the patient was hemodynamically stable. Patients with a red blood cell count of more than 100,000/mL or a white blood cell count of more than 500/mL, or clinical or radiographic evidence of visceral injury requiring repair underwent exploratory celiotomy. If a pelvic hematoma was present it was not entered. Patients with unstable or displaced pelvic fractures had an external fixator applied in the operating room. If this did not control bleeding in the pelvis, or if the volume of bleeding was too great to respond to osseous fixation, arteriography was performed in angiography. Actively bleeding vessels were embolized with autologous clot, gelatin sponge, or coils.

All data were recorded on a custom database on an IBM personal computer (Armonk, NY). Statistical analysis was performed using SAS software (SAS Institute Inc., Cary, NC) running on an IBM mainframe computer. Continuous data were tested by t tests, analysis of variance, or regression analysis, as appropriate. Categoric data were evaluated by chi square tests. Multivariate multiple regression (canonical) analysis was used to calculate the individual and collective contribution of multiple independent factors on combined outcome criteria. A type I error probability of 0.05 was established as the minimal level of significance.

Results

During the 48-month period of review, 305 patients with pelvic fractures were admitted to UMC. Sixty-nine patients were excluded for the following reasons: 34 were transferred from another hospital from 1 to 60 days after injury; 19 patients had a fracture of the acetabular labrum or an avulsion fracture as the only pelvic fracture; 8 had penetrating wounds of the bony pelvis; 6 patients had pathologic fractures. Two records could not be found. Of the remaining 236 patients, there were 144 men (61%) and 92 women; their mean age was 31.5 years (range, 1 to 86 years). Almost two thirds were injured in motor vehicle accidents, and only one of these—an elderly man with a fracture of the dome of the acetabulum—was wearing a seatbelt. Thirty-three pedestrians were struck by a motor vehicle, 16 patients were crushed, 12 each were injured in motorcycle accidents or falls, and 11 were injured in miscellaneous accidents (bicycle *versus* motor vehicle, all-terrain vehicle, and boating accidents). The mean ISS was 21.3. Blood transfusions were not needed in 85 patients (36%). The 151 patients who required blood

TABLE 1. *Patient Characteristics by Mechanism of Injury*

Mechanism	Motor Vehicle	MV–Pedestrian	Crush	Motorcycle	Fall	Miscellaneous
Number (%)	152 (64.4)	33 (14)	16 (6.8)	12 (5.1)	12 (5.1)	11 (4.6)
Age (yrs)	30.4	32.0	44.2*	27.6	45.9*	17.6
Revised trauma score	11.0	10.3	11.8	10.8	11.9	11.4
ISS	21.6	26.2	17.4*	21.4	12.1*	17.4
Units of blood in first 48 hours	4.8	6.7	4.4	8.2	2.9*	1.8*
Hospital days	16.9	16.8	17.8	20.4	13.7	13.2
Hospital charges	$18,348	$18,437	$17,251	$25,692	$8182	$13,196
Deaths (% of group)	10 (6.6)	5 (15.2)	0 (0)	2 (16.7)	1 (8.3)	0 (0)

* $p < 0.05$.

ISS, Injury Severity Score; MV, motor vehicle.

received 1 to 48 units, with a mean transfusion volume of 7.8 units. Hospital stay averaged 16.8 days.

When examined by mechanism of injury (Table 1), patients injured in falls and crushing accidents tended to be older and had lower ISS values and smaller transfusion requirements than other patients. Those with injuries from miscellaneous causes were younger than the other patients because this group included several children injured in bicycle-motor vehicle collisions. Their ISS values and the number of units of blood administered to them were less than in patients in motor vehicle, motorcycle, or motor vehicle *versus* pedestrian accidents. The greatest probability of death was in the last two categories, but the differences in mortality rates were not significant. There were no significant differences among the groups with regard to revised Trauma Score, hospital charges, or duration of hospital stay.

Eighteen of the 236 patients died (mortality rate, 7.6%), and of these, seven deaths (38.9%) were caused by hemorrhage. One patient with a severely comminuted open pelvic fracture died of irreversible shock from pelvic exsanguination, despite successful embolization of an arteriographically demonstrated bleeding vessel. Five patients died from abdominal hemorrhage caused by massive visceral or vascular injuries, and one patient exsanguinated from a traumatic above-knee amputation with contralateral open fractures of the femur and tibia. Of the 11 deaths not caused by hemorrhage, 5 patients died from head injuries, 2 died of sepsis, 2 from multiple-organ failure, 1 from respiratory failure due to a severe pulmonary contusion, and 1 from a pulmonary embolus, despite appropriate prophylaxis. Only one of the patients whose death was caused by abdominal hemorrhage had a pelvic hematoma, but the volume of blood in the pelvis was small compared to the massive blood loss from rupture of the abdominal aorta. None of the deaths from sepsis or multiple-organ failure were related to the pelvic fracture. All four patients had major cavitary hemorrhage and a head injury; their pelvic hematomas were small or nonexistent.

Nine patients with severe hemorrhage underwent arteriography for evaluation of suspected bleeding from the pelvic fracture. Only three of them had active bleeding from a pelvic vessel, and these were embolized successfully. Two patients survived and one died of irreversible shock. All six patients without active pelvic bleeding survived; all of them had a pelvic hematoma, but three were only small or moderate in size. Of the nine patients who underwent pelvic arteriography, seven had significant intra-abdominal bleeding that required celiotomy for control. Injuries were to the spleen (3 patients), liver (3 patients), and small bowel mesentery (2 patients). Three patients had pelvic arteriograms before peritoneal lavage because their bleeding was thought to be from their severe pelvic fractures. Arteriograms were negative in all three, but celiac and mesenteric injections were not performed. Eight of the nine patients in whom pelvic arteriograms were obtained developed a coagulopathy because of major hemorrhage and volume replacement, and their coagulopathy probably contributed to small-vessel and medullary bleeding into the pelvis.

Indices of injury severity were analyzed with regard to the following aspects of the pelvic fractures: anatomic site, vector of injury, maximal fracture displacement, and stability. Patients with fractures in multiple geographic areas of the pelvis had more severe injuries than patients with fractures in only one area. The only exceptions were that patients with acetabular fractures had higher AIS scores for the face than did patients with multiple fractures, and there were no differences among groups in Glasgow Coma Score or AIS scores for the head/neck and external systems. Patients whose pelvic fractures were confined to the acetabulum, ilium, pubis, or ischium had very similar values for all criteria of injury severity.

Compared to those with anterior–posterior compression, impaction, and unknown vectors of injury, patients with multiple force injuries had the highest requirement for crystalloid resuscitation, the lowest systolic blood pressure, the greatest hospital charges, and the longest duration of hospitalization ($p \leq 0.03$). Along with patients with vertical shear injuries, they also had the highest AIS scores for the abdomen and the highest ISS values ($p \leq 0.0001$). Other differences among groups were not great, and because of large variances were not statistically significant. There were no significant differences in any of the injury severity criteria between patients with lateral compression, vertical shear, or multiple force injuries.

The amount of displacement of the pelvic fracture was roughly correlated with injury severity criteria, but the differences were inconsistent and were primarily between patients with no fracture displacement and those with either moderate or severe displacement. Instability of the pelvic fracture was the best predictor of injury severity. As shown in Table 2, there were substantial differences between patients with stable pelvic fractures and those with unstable fractures, with the latter having more severe associated injuries.

Multivariate multiple regression analysis demonstrated that stability of the pelvis had the highest correlation with injury severity criteria ($r = 0.56$, $p < 0.0001$). Site(s) of the fracture had the next highest correlation ($r = 0.51$, $p < 0.001$), but its predictive ability was reduced because it could distinguish only between patients with fractures in either one anatomic area of the pelvis or fractures in more than one area. Correlations of injury severity with displacement of the fracture ($r = 0.41$, $p < 0.005$) and with the vector of injury ($r = 0.42$, $p < 0.01$) were significant but contributed little to predictive capability. If site and stability of the pelvic fracture were known, their combined correlation with injury severity criteria was increased slightly to 0.59 ($p < 0.0001$). Adding displacement did not improve prediction ($r = 0.60$, $p < 0.0001$). Similarly, if displacement and stability were known ($r = 0.59$, $p < 0.0001$), adding vector of injury did not alter the ability to predict injury severity ($r = 0.58$, $p < 0.0001$). Because of a close relationship between fracture site and vector of injury, it was not possible technically to evaluate by canonical analysis any contribution of these two variables in combination to predicting injury severity.

TABLE 2. *Injury Severity Criteria and Pelvic Fracture Stability*

Criteria	Stable	Unstable
Systolic BP	114.1	101.8*
Glasgow Coma Score	13.8	13.6
Revised Trauma Score	11.1	10.6
Units of blood in first 48 hours	2.6	5.6*
Crystalloid volume (mL)	1477.0	2668.4*
ICU days	1.1	3.7*
Hospital days	14.8	22.5*
Hospital charges	$14,051.8	$28,720.2*
AIS, abdomen	0.67	1.93*
AIS, chest	0.91	1.33*
AIS, extremities	2.72	3.81*
AIS, face	0.41	0.26
AIS, head/neck	1.13	1.43
AIS, external	0.96	1.08
ISS	18.08	29.67*

* $p < 0.05$.
BP, blood pressure; ICU, intensive care unit; AIS, Abbreviated Injury Scale; ISS, Injury Severity Score.

TABLE 3. *Injury Severity Criteria and Discharge Site*

	Discharge Site		
Criteria	Home	Other*	Death
Systolic BP	114.4	104.3	74.1†
Glasgow Coma Score	14.2	12.9	8.8†
Revised Trauma Score	11.4	10.0	6.9†
Units of blood in first 48 hours	2.1	5.7	17.4†
Crystalloid volume (mL)	1583.0	2728.9‡	3429.0†
ICU days	1.4	2.8	4.7‡
Hospital days	17.0	29.7‡	6.1†
Hospital charges	$16,582.7	$32,773.0‡	$24,543.8
AIS, abdomen	0.91	0.83	2.12‡
AIS, chest	0.89	2.08‡	1.82‡
AIS, extremities	2.94	3.50‡	3.41‡
AIS, face	0.30	0.58	1.12‡
AIS, head/neck	1.01	1.92	3.00‡
AIS, external	0.94	1.50	1.35
ISS	18.54	29.75‡	45.24†

* Other: rehabilitation facility, nursing home, or other hospital.
† Different from home, other.
‡ Different from home.
BP, blood pressure; ICU, intensive care unit; AIS, Abbreviated Injury Scale; ISS, Injury Severity Score.

As would be expected, final disposition was closely related to indices of injury severity (Table 3). Patients who died had the most severe injuries, those who were discharged to home had less severe anatomic injuries and physiologic derangements, and those who were discharged to a rehabilitation facility or to a nursing home tended to have injuries of intermediate severity. When outcome was evaluated with regard to the severity of the pelvic fracture, there was no association between any aspect of the pelvic fracture and final disposition. Vector of injury ($p = 0.29$), amount of fracture displacement ($p = 0.57$), site of pelvic fracture ($p = 0.77$), and pelvic stability ($p = 0.94$), either individually or collectively, could not predict whether a patient would live, die, or have a significant disability.

Discussion

Pelvic fracture has been recognized for decades as a serious injury associated with high mortality rates. The considerable forces that are required to fracture the pelvis also involve other areas of the body, resulting in many associated injuries. Despite these injuries, massive hemorrhage within the pelvis has received a great deal of attention as one of the major consequences of pelvic fractures. This bleeding can originate from exposed cancellous bone and injured soft tissue at the fracture sites, or from veins or arteries that traverse the pelvis. Under normal circumstances the blood is contained within the pelvis between the parietal peritoneum superiorly and the strong fibromuscular and bony walls of the pelvis. If these barriers are violated by the wounding forces or at surgery, the bleeding no longer will be contained and exsanguination can occur. This accounts for the high mortality rate associated with open pelvic fractures[7,8] and also for the dismal results associated with attempts to achieve hemostasis by either direct surgical control of bleeding vessels or bilateral hypogastric artery ligation. Despite initial enthusiasm for these techniques,[9,10] individual ligation of bleeding vessels in pelvic hematomas is almost never technically feasible,[11] and attempts to do so will breach the peritoneum, which contains the hematoma. The rich collateral flow of blood within the pelvis prevents hypogastric artery ligation from being effective. More than 20 years ago Burchell[12] showed that ligation of both hypogastric arteries reduced mean arterial pressure in the distal arteries by only 24%, and on the basis of a review of the literature, Patterson and Morton[13] concluded that hypogastric artery ligation was of no value in the control of hemorrhage associated with pelvic fractures.

Pneumatic antishock garments[14] and fracture fixation with an external frame[15] have been promoted as techniques to reduce bleeding from pelvic fractures by providing tamponade, apposing the fracture fragments, and reducing the volume of the pelvis. The placement of packs would have similar effects but would require a celiotomy and secondary operations to remove the packs. Although these techniques are clearly helpful in some patients with significant hemorrhage from pelvic fractures, when bleeding originates from major arteries the only effective technique is a direct approach to the vessels. As stated above, a direct surgical approach is neither easy nor wise, but a transvascular approach allows the surgeon to avoid the problems inherent in entering the hematoma. Angiographic demonstration and control of bleeding from pelvic fractures was first proposed by Athanasoulis et al.[16] in 1971, and following its first reported use in 1972 by Margolies et al.,[17] this technique has become the standard approach for control of persistent arterial bleeding associated with pelvic fractures. Although successful embolization and control of pelvic hemorrhage can be achieved, the reported mortality rate following transcatheter embolization varies from 35% to 89%.[18-22] Most of the deaths are caused by associated injuries, not by the pelvic fracture. When embolization failure occurs, it is almost always in association with a severe secondary coagulopathy.

Cryer et al.[1] tried to predict the probability of major bleeding in pelvic fractures by classifying them into discrete categories of 'stable' or 'unstable.' They defined instability as a gap or displacement of the pelvic fracture of more than 0.5 cm, without regard to whether there was any mechanical instability of the pelvis. They found that they could predict with 90% certainty that 50% to 69% of patients with an unstable pelvic fracture would require at least a four-unit blood transfusion. Nearly one half of the patients with an unstable pelvic fracture had an associated intra-abdominal injury. When these patients were excluded from analysis, the authors reported that there was still 'a moderate to good correlation'[1] between pelvic fracture instability and blood transfusion requirements, but certainly some of the blood losses in their patients were from extrapelvic sites of injury. Furthermore their classification system did not define a group of patients with pelvic fractures who were not at risk for major bleeding because up to one fourth of patients with stable pelvic fractures would need four or more units of blood.

Trunkey et al.[23] showed that more severe pelvic fracture patterns are associated with a greater number and severity of associated injuries. Similar conclusions were reached by other investigators[24-26] using classification schemes of varying complexity. The common determinant of injury severity and morbidity in each of these studies was instability of the pelvic fracture, but most of the deaths in their patients were caused by associated injuries and were not due to the pelvic fracture.

In this study we corroborate that the pelvic fracture is a marker of injury severity and further demonstrated that the pelvic fracture, regardless of severity, does not determine the final outcome. Most pelvic fractures are relatively straightforward and require no specific treatment other than bedrest and analgesics. These fractures are usually caused by low-intensity forces and are associated with few and relatively minor injuries to other anatomic areas. Larger forces from high-speed motor vehicle accidents or crushing injuries result in increased pelvic fracture complexity, which is correlated with an increased risk of complications and a greater probability of more severe associated injuries.

The number of anatomic units of the pelvis that have been fractured and the amount of displacement of those fractures can be determined easily by a review of standard pelvic roentgenograms, with little interobserver variability for these parameters. Pelvic fractures that involve multiple areas of the pelvis and greater amounts of displacement of the fractures are associated with more severe injuries to other areas of the body. These more complex fractures are more likely to be mechanically unstable, and the highest correlate of injury severity is the presence of pelvic instability. Loss of stability by disruption of the strong posterior elements of the pelvic arch requires the transmission of major forces to the pelvis, and this is associated with the delivery of similar forces to other areas of the body, especially the head, chest, and abdomen. The severity of injuries to these areas determines the outcome from injury in most patients. Stability or instability of the pelvis can be implied from pelvic roentgenograms, but this is also a clinical determination that usually is readily apparent. It is somewhat more difficult to categorize the mechanistic vector of injury to the pelvis. The classification system first proposed by Pennal and Sutherland[27] has been modified to enhance its precision and has been very useful in explaining the patterns of fractures associated with various directions of energy transmission to the pelvis. Dalal et al.[25] developed an elaborate classification system for pelvic fractures based on vector and severity of injury to the pelvis. They reported that the mechanism (vector) of injury was related to the pattern of associated organ injuries, blood losses, and outcome. Unfortunately not all pelvic fractures can be classified accurately as to vector of injury; there is a moderate degree of variability of classification among observers. This probably accounts for the lower correlations that we observed between injury vector and injury severity criteria than with other aspects of the pelvic fracture. It is noteworthy that the most severe pelvic fractures in the series reported by Dalal et al.[25] were also the most unstable, emphasizing the fact that loss of pelvic stability is highly correlated with overall injury severity, as we demonstrated.

The fact that indices of severity of the pelvic fracture correlated with indices of injury severity, but not with final hospital outcome was an unexpected finding. This emphasizes that a diligent search must be made for other injuries in patients with pelvic fractures, and the more severe the pelvic fracture, the more likely the patient will have severe injuries to other anatomic areas. These injuries usually can be identified by physical examination and standard diagnostic studies in the trauma patient, such as chest roentgenograms, peritoneal lavage, or computed tomography. Unless the patient is clearly bleeding from the pelvis, and not from some other site, these injuries must take priority over the pelvic fracture. This approach is supported by Moreno et al.[2] and by Evers et al.,[18] who advocated celiotomy in all patients with pelvic fractures who have grossly positive peritoneal lavage. When the lavage is negative, or is positive by red cell count, they recommended that patients who were hemodynamically unstable should have the pelvis stabilized by placement of an external frame. Patients who continued to have pelvic bleeding after this maneuver should undergo arteriography.

Massive hemorrhage from the pelvis almost invariably originates from named arteries. Although tamponade with a pneumatic antishock garment or fracture stabilization with an external fixator may provide some benefit, all of these patients will require arteriography, with embolization of actively bleeding vessels. Such injuries are uncommon and usually seen with open pelvic fractures. Patients with relatively large pelvic hematomas often have normal pelvic arteriograms with no evidence of ongoing hemorrhage. This may be due to tamponade of the bleeding by a contained hematoma, but in our experience this scenario often is caused by a coagulopathy due to major cavitary hemorrhage, shock, and hypothermia. The pelvic hemorrhage is from cancellous bone and the surrounding soft tissues. It cannot be identified by arteriography and persists because of the coagulopathy. The appropriate treatment is to search for and control bleeding from the chest, abdomen, or other sites while simultaneously resuscitating the patient from shock and replacing platelets and coagulation proteins. Warming intravenous fluids in the trauma room is important to prevent or reverse hypothermia, which contributes to coagulopathy, but the best way to warm the patient is to restore visceral perfusion and thereby support metabolism. Early pelvic fracture stabilization should be performed to prevent the complications of prolonged bedrest. Although the application of an external frame might reduce the amount of bleeding from cancellous bone, it cannot be expected to provide significant benefit if the bleeding originates from major pelvic vessels or continues because of a coagulopathy.

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DISCUSSIONS

DR. LOUIS BRITT (Memphis, Tennessee): Dr. Rhodes has done an outstanding job, not only in analyzing these patients but also in presenting this unbelievable mass of data. I think you are to be congratulated on your mortality rate of 7%, which is about one half that reported by Drs. Fabian and Fox from our institution.

I am uncertain about the cause of this. We think this discrepancy is either because you are better doctors or there is a problem in our classification. Would you define what you consider an open pelvic fracture? Because 43% of our pelvic fractures were open; therefore the bleeding, and so forth, was into other areas.

Second I certainly agree, and it has been our experience that most deaths have been due to associated injuries. You stated in your conclusions that the major hemorrhage comes from named arteries. You only had three named arteries embolized in 9 of 239 patients arteriogramed. I think this leads us to the issue that we have all talked a great deal about: arterial embolization and pelvic angiography.

I wonder if you could tell me what the place of this is, not only in the diagnosis but also in the treatment of these patients. Sometimes we get involved with the technology and our good sense gets away from us.

Finally we have found something that we think is very significant in the last couple of years, and that is external fixation. We believe this has reduced the pelvic hemorrhage.

One of the most important things Dr. Rhodes has done, in addition to a lot of hard work, is that he has stressed that the pelvic fracture does not kill patients; rather it is the associated injuries that cause deaths. And when patients are in shock we should look outside the pelvis for another source of hemorrhage.

DR. ANTHONY MEYER (Chapel Hill, North Carolina): I would like to congratulate the authors on an excellent paper and the use of multivariate analysis to try to identify the factors that contribute to survival from pelvic fractures.

I have three questions. First what criteria did you use for arteriography: absolute blood loss, rate of transfusions, or any evidence of hemodynamic instability?

Second did you have any protocols for either the evaluation, such as using abdominal or pelvic computed tomography or treatment, such as when you would use external fixation?

Third what was the frequency of severe coagulopathy or profound hypothermia in your series overall? Because these are, obviously, contributing factors in these patients, as you mentioned, on whom did you perform arteriography?

One of the things that struck me the most was the fact that only one of those patients was wearing a seat belt, which might prompt some question as to the value of seat belts for vehicular passengers.

DR. LEWIS FLINT (New Orleans, Louisiana): Let me preface my questions by stating that on two previous occasions we presented data concerning pelvic fractures to this group. The last time was this past year. And in both of those presentations, we stressed the use of a multimodality evaluation approach that identified in priority those sites of bleeding outside the pelvis, followed by the injuries that are common to the genitourinary system, then the pelvic bleeding.

In your manuscript, it implies, at least, that you took a different approach, in that you tried to identify the pelvic bleeding site before you identified the extrapelvic bleeding sites.

We think that may be the wrong order in which to do things, and I wonder if the coagulopathy that you implied was a contributor to the pelvic hemorrhage in some of your patients may have been encountered because of delay in dealing with the extrapelvic bleeding sites.

I'm not quite sure—maybe you can clarify for me—what is the bottom-line message of your paper. If it is that we need to have a highly disciplined approach to these injuries and that extrapelvic bleeding sites are important determinants of the outcome, then I agree with you completely.

But if your thesis is that the site of the bleeding in the pelvis is not important a factor in the outcome of these injuries, then we have some grounds for disagreement. Perhaps you could clarify that in your closing.

DR. GALEN V. POOLE (Closing discussion): Dr. Britt, I do not think that the difference in mortality rate has anything to do with the quality of the physicians. To some extent it may be because we were very vigorous in identifying all patients with pelvic fractures, even those with fairly minor injuries to the pubic rami and things of that nature, which may not have been coded in your own series or those of others or may not have been included although they were identified. We may have had a larger proportion of relatively minor injuries that would not be associated with significant injuries to nonpelvic sites.

An open fracture, by our definition, was one that involved the overlying skin, the rectum, or the vagina. We did not include those that involved the bladder or other areas of the genitourinary system because, in most circumstances, those areas would be sterile. There would be very little contamination that would involve them, and patients were not likely to have a greater incidence of death from pelvic hemorrhage if they had an injury to the bladder compared to those with other closed fractures.

You asked what the role of hemorrhage was and how we identified the patients who would have arteriography.

If a patient seemed to be bleeding to death, had no blood in the chest, no external sites of hemorrhage from extremities, a negative lavage or lavage that was positive only by counts, then that was a patient who probably was bleeding into the pelvis.

This is not new information, and we are not trying to present anything revolutionary. We are re-emphasizing the importance of what will cause death in these patients.

You did mention the use of external fixation. We have used external fixation for a number of years. Our orthopedic surgeons are, in general, very keen on the use of external fixation to improve stability and slow bleeding. In all honesty, I have no data to suggest that this may be effective, and it may even be true that it has no effect or only a minimal effect, especially in patients whose bleeding is arising from large arteries.

Dr. Meyer asked what criteria we used for arteriography, and I hope that I have clarified that in my answer to Dr. Britt's question. If there is no evidence of nonpelvic hemorrhage and the patient appears to be bleeding to death or is in significant hemorrhagic shock, those patients need an arteriogram. And I am not sure that an external fixator will help them; not if they are bleeding from the pudendal artery or a gluteal or one of the other major vessels in the pelvis.

External fixation was used primarily when it appeared that the pelvic fracture was grossly unstable mechanically. There was no other protocol or criteria that we used to select external fixation, but it was used fairly frequently.

The overall incidence of coagulopathy in the entire series was about 5% to 6%. These patients were usually the ones who were more seriously injured and had lost significant volumes of blood, but the blood may not have been lost into the pelvis. It was often from nonpelvic sites. And when they developed hemorrhagic shock with poor tissue perfusion, they clearly developed coagulopathy because of hypothermia and the replacement of blood with asanguinous fluids as well as banked blood.

Dr. Meyer also mentioned that only one of those patients was wearing a seat belt. I would remind the audience that the state of Mississippi has the lowest percentage of seat belt use of any state in the union, only 17%. This is a problem that we deal with every day, unfortunately.

In answer to Dr. Flint's questions, I do not think we really disagree. I think we have just used a slightly different approach. We also stressed a multimodality approach in these patients. And although he may have thought that we were looking for pelvic hemorrhage before we looked for other sites of hemorrhage, that is really not the case.

There were three patients in whom there were protocol violations, although these were not done under strict protocol; it was more of a commonsense judgment. But these three patients were taken to the arteriogram suite, had arteriography, had no sites of pelvic hemorrhage, and then someone decided that perhaps we should have done a lavage earlier. Those were clearly errors on our part in management. They occurred in the heat of battle, often with some inexperienced residents who may not have been communicating as well as they should have. But, in general, patients were evaluated with lavage or computed tomographic scanning to address abdominal hemorrhage before any pelvic sites were evaluated.

The bottom line is simply that you cannot ignore the abdomen as a site of major hemorrhage. You cannot ignore the chest or the importance of head injuries in these patients, who are usually injured in motor vehicle accidents or by other blunt forces with which they are very likely to have injuries outside of the pelvis, which really determines their outcome.

Factors Affecting Morbidity Following Hepatic Trauma

A Prospective Analysis of 482 Injuries

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During a 5-year period, 482 patients with liver injuries were studied prospectively: 65% resulted from penetrating and 35% from blunt injuries. The injuries were graded by the hepatic injury scale (grades I to VI); transfusion requirements and perihepatic abscesses correlated with increasing scores. Minor surgical techniques were needed in 338 patients and 144 patients required major techniques. Omental packing was used in 60% of the major injuries and yielded 7% mortality and 8% abscess rates. Gauze packs were used for management of 10% of major injuries and yielded 29% mortality and 30% abscess rates. The patients were randomized to no drain, closed suction, or sump drainage and respective perihepatic abscess rates were 6.7%, 3.5%, and 13% ($p < 0.03$; suction compared to closed suction). Multivariate analysis demonstrated increasing abdominal trauma indices and transfusion requirements as well as sump drainage to be associated independently with perihepatic infection.

REDUCING THE MORBIDITY and mortality from hemorrhagic shock and subsequent sepsis remain the main obstacles in the management of liver trauma. Many approaches for operative management of complex liver injuries are used, including packing techniques, resectional debridement, and hepatotomy with vascular ligation. Recent reports implicated clinical parameters, including shock, transfusion, severity of liver injuries, and associated injuries, as predisposing factors for septic complications.[1-4] Not only has the optimal type of hepatic drainage been questioned, indeed, whether any drainage is of value remains unresolved.[5-7] The purpose of this study was to evaluate the efficacy of our surgical approach with particular emphasis on liver injury-related sepsis. Closed suction, sump, and no drainage were applied randomly in an attempt to resolve the issue of the optimal drainage technique.

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Materials and Methods

From November 1985 to October 1990, all patients with liver injury admitted to the Presley Regional Trauma Center following penetrating or blunt trauma were evaluated prospectively. Severity of liver injury was graded according to the American Association for the Surgery of Trauma (AAST) Hepatic Injury Scale (Table 1).[8] Analysis of morbidity included presence of perihepatic abscess, bile leak by 99m Tc-dimethyl iminodiacetic acid (HIDA) scan, and length of hospitalization. Risks analyzed for morbidity included mechanism and severity of injury, transfusion requirements, operative management, presence of hollow viscus injury, and method of drainage. Patients who died within 48 hours of admission were excluded from all morbidity analyses but all were evaluated for mortality.

All patients with gunshot wounds to the torso inferior to the nipple line and superior to the inguinal creases underwent abdominal exploration. Stable patients with anterior stab wounds underwent local exploration followed by laparotomy if the anterior fascia was violated. Stable patients with stab wounds to the back or flank were initially observed and serially examined; they received laparotomy if they became unstable or developed abdominal tenderness. Following blunt trauma, indications for abdominal exploration included a positive diagnostic peritoneal lavage, abdominal computed tomography (CT) demonstrating intra-abdominal injury, or abdominal tenderness on physical examination.

Our institutional approach to operative management of liver injuries is as follows: initially the falciform ligament is divided and the anterior surface inspected. Laparotomy pads are used to pack the liver while the rest of

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TABLE 1. *Liver Injury Scale*

Grade*		Injury Description†
I	Hematoma	Subcapsular, nonexpanding, <10% surface area
	Laceration	Capsular tear, nonbleeding, <1 cm parenchymal depth
II	Hematoma	Subcapsular, nonexpanding, 10%–50% surface area
	Laceration	Capsular tear, active bleeding; 1–3 cm parenchymal depth, <10 cm in length
III	Hematoma	Subcapsular, >50% surface area or expanding; ruptured subcapsular hematoma with active bleeding; intraparenchymal hematoma >2 cm or expanding
	Laceration	>3 cm parenchymal depth
IV	Hematoma	Ruptured intraparenchymal hematoma with active bleeding
	Laceration	Parenchymal disruption involving 25%–50% of hepatic lobe
V	Laceration	Parenchymal disruption involving <50% of hepatic lobe
	Vascular	Juxtahepatic venous injuries; *i.e.*, retrohepatic vena cava/major hepatic veins
VI	Vascular	Hepatic avulsion

* Advance one grade for multiple injuries to the same organ.

† Based on most accurate assessment at autopsy, laparotomy, or radiologic study.

the abdomen is explored. The right lobe is mobilized completely by dividing the right triangular and coronary ligaments. The left lateral segment is similarly mobilized if necessary. In some cases compression of the porta hepatis (Pringle maneuver) is helpful for temporarily control of hemorrhage. Hemorrhage is controlled initially with direct pressure, then individual bleeding vessels are identified and ligated. Deep mattress sutures are not used for hemostasis. All injuries with obvious arterial hemorrhage are explored. Hepatotomy is indicated for deep penetrating injuries when either arterial hemorrhage or profuse venous bleeding is present. Prompt definitive therapy then is performed to avoid coagulopathy associated with continued blood loss and hypothermia.

Definitive operative management of the liver injury was classified as either minor or major. Minor therapy included topical hemostatic techniques (including local pressure on the liver with laparotomy packs or topical hemostatic agents), electrocautery, and individual suture of superficial bleeding vessels. Minor therapy was used almost exclusively for grades I and II injuries. Major therapy included omental packing (which required at least grade III injury), individual suture of large vessels within hepatic parenchyma, resectional debridement, and gauze packing. Omental packing was used in patients with deep lacerations (at least three cm deep), stellate fractures, and burst injuries. After all bleeding vessels are individually ligated, omentum is packed into the hepatic defect after mobilization off the transverse colon. Care is taken to avoid damaging the vascular pedicle. Bleeding from the defect is controlled by omental tamponade; the omentum is then sutured into place with running polypropylene suture. Only patients with severe liver and/or associated injuries who developed intraoperative coagulopathy received gauze packing to prevent exsanguination. Tamponade of hemorrhage is achieved by placing laparotomy packs anterior and posterior to the bleeding liver and then closing the abdomen. All survivors with gauze packing returned to the operating room (after the coagulopathy and hypothermia were corrected) 24 hours after the initial procedure for pack removal. If technically possible, omental packing then was performed.

During the first half of the study, patients were randomized to receive either sump drains (date of admission an even number) or no drain (date of admission an odd number). During the second half of the study, patients were randomized to receive either closed suction drains or no drain by the same randomization scheme. Thus one half of the patients had no drainage, and the others had one of the two drainage techniques. When the daily drainage was less than 20 mL (usually 3 to 6 days after operation), closed suction drains were removed. Sump drains were advanced 2 to 3 cm per day when the drainage was less than 20 mL per day. Gradual removal was accomplished during a few days to allow the potentially colonized tract to heal from the inside out.

As part of the protocol, patients received HIDA scans on postoperative days 5, 6, or 7 to determine the presence or absence of bile leak. Scans were examined for the following details: space-occupying lesions (hematoma, abscess), or abnormal bile collections. A bile leak was defined as any bile collection, either intrahepatic or extrahepatic. Early deaths or those patients discharged from the hospital before postoperative day 5 did not have HIDA scans.

Liver-related complications were defined as either perihepatic abscesses or bile leaks. Perihepatic abscesses included all purulent collections in the right subphrenic space, subhepatic space, or within hepatic parenchyma. Bile leaks were determined by HIDA scan and were included as complications when their presence necessitated drainage. Indications for drainage included persistent fever, abdominal pain, and a well-defined collection seen on CT scan. All patients with liver complications underwent operation or had CT-guided percutaneous drainage.

Statistical Analysis

Discrete (categorical) variables were analyzed with the chi square test of homogeneity or Fisher's Exact test and all continuous variables with either the analysis of variance or the Kruskel-Wallis test. Lengths of hospital stay for patients in the three treatment arms were compared with rank tests for homogeneity among types of drain. Other tests for homogeneity over drain types were made for all confounding variables. Statistical significance was considered at $p < 0.05$. Because patient variables, indicators of severity of injury, and hepatic injury grade could act as confounding variables, we controlled for these using multiple logistic regression analysis. For each risk factor, we compared risk ratios estimated in the presence of a potential confounder to that estimated in the absence of potential confounders. Because the presence of the type of drain or absence of a drain could act as multiple risk factors, we used multiple logistic regression to identify multiple potential risk factors.

Results

There were 482 patients with liver injuries managed during the 5-year period. Blunt trauma occurred in 168 patients (35%) and penetrating trauma in 314 patients (65%). Motor vehicle accidents, pedestrians struck by moving vehicles, and falls or assaults occurred in 88%, 6%, and 6%, respectively, of the blunt injury patients. Of the penetrating injury group, 60% were gunshot wounds, 37% were stab wounds, and 3% were shotgun blasts. Sixty-four per cent of the blunt injury patients were male, compared to 87% of the penetrating injury patients. The average age of the patients was 29 years (range, 11 to 79 years).

Liver Injury-associated Complications

There were 34 patients who developed perihepatic abscesses following injury, an incidence of 7% of the total population. Forty-four per cent followed blunt injury and 56% occurred after penetrating injury. Abscesses were confined to the right subphrenic (11) or subhepatic spaces (18) or were intrahepatic (5). All were considered direct complications of the liver injury, were confirmed by CT scan, and required either surgical (25) or CT-guided (9) drainage. There were three deaths from sepsis and multiple-organ failure attributable to these abscesses. The following isolates were obtained: *Staphylococcus aureus* (7), *Staphylococcus epidermidis* (5), Streptococcal species (7), Enterococcus (8), *Escherichia coli* (4), Enterobacter species (7), *Pseudomonas aeruginosa* (5), other gram-negative rods (5), gram-positive rods (5), Bacteroides species (7), and *Candida albicans* (5). Five collections had no growth.

Figure 1 illustrates the results of the HIDA scans obtained in 228 patients. Sixty-three patients demonstrated a bile leak; 51 communicated with small cavities that resolved spontaneously, and 12 (19%) communicated with a perihepatic abscess. One hundred sixty-five patients exhibited no bile leak on HIDA scan and 17 patients (10%) developed a perihepatic abscess. Although not statistically significant ($p < 0.08$), these data suggest a correlation between bile leak and perihepatic abscess.

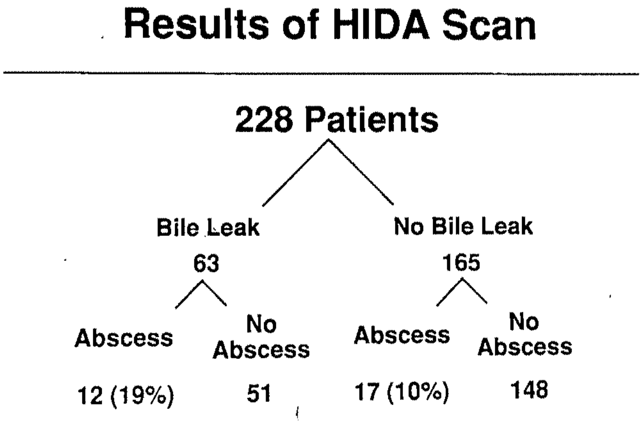

FIG. 1. Summary of HIDA scan results and correlation with perihepatic abscess formation.

Hepatic Injury Grading

The severity of liver injury was stratified by the hepatic injury grading system (Table 1). Fifty-five patients (11%) were grade I, 171 (35%) were grade II, 180 (37%) were grade III, 42 (9%) were grade IV, 28 (6%) were grade V, and six (1%) were grade VI. The mean transfusion requirements in units for the liver injury grades I to VI were 1.9, 3.2, 4.4, 10.3, 12.6, and 32.7, respectively. Figure 2 demonstrates the frequency distribution of the hepatic injury grades in the total population, and also illustrates the incidence of perihepatic abscess in each grade. There is a linear progression of transfusion requirements and abscess with increasing liver injury grades.

Surgical Management

Operative management was analyzed according to minor and major liver injuries. Management of 338 minor injuries (70% of total) included cautery in 115, topical in 165, or suture (superficial vessels) in 58. Major injury (30%) management involved omental packing in 87, resectional debridement in 20, suture (larger vessels within hepatic parenchyma) in 23, and gauze packing in 14. Mean transfusion requirements for minor injuries were 3.1 units. Omental packs required 6.0 units, resectional debridement 12.1, major suture 13.6, and gauze packing 22.6 units. Twenty-eight per cent of minor injuries were caused by blunt injury and 72% by penetrating. Fifty-one per cent of major injuries were blunt and 49% were penetrating. An overview of the outcome according to type of operative management is reported in Table 2. The incidences of both perihepatic abscess and bile leak were twice as high in those with major injuries compared to minor injuries. There were no liver-related deaths in those

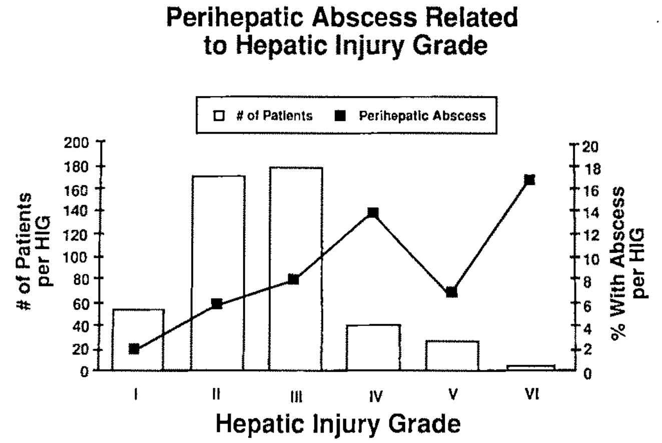

FIG. 2. Distribution of hepatic injury grades and perihepatic abscess frequency by injury grade.

with minor injuries, but major injury had a 10% mortality rate. Omental packing was the most common procedure used for major hepatic injuries (60%) and provided relatively low septic morbidity and mortality rates of 8% and 7%, respectively. The use of gauze packing in the bleeding patient resulted in a 30% incidence of perihepatic abscess and a 29% mortality rate.

Drainage Groups

Excluding 10 early deaths, there were 472 patients evaluable for the outcome of liver drainage technique. They were randomized to 255 instances of no drainage, 102 sump drainage, and 115 closed suction drainage. The relative increase in the no drain group is due to the fact that 20 patients with minor injuries (grades I and II) had protocol violations and were not drained. The frequency distribution of the drainage groups according to the grading scale are illustrated in Figure 3.

The drainage groups were evaluated for comparability according to age, Injury Severity Score (ISS) (blunt only), Abdominal Trauma Index (ATI), admission blood pressure, hepatic injury grade, mechanism of injury, presence of hollow viscus injury, and transfusion requirements.

TABLE 2. *Operative Management and Complications*

Method of Repair (N)	Number in Group with Complications (%)	
	Perihepatic Abscess*	Liver-related Mortality
Minor (338)	19 (5)	0 (0)
Major (144)	15 (14)	11 (10)
Omental pack (87)	7 (8)	6 (7)
Gauze pack (14)	3 (30)	4 (29)
Resection (20)	3 (15%)	1 (5)
Suture (23)	3 (14)	3 (13)

* Excluding early deaths.

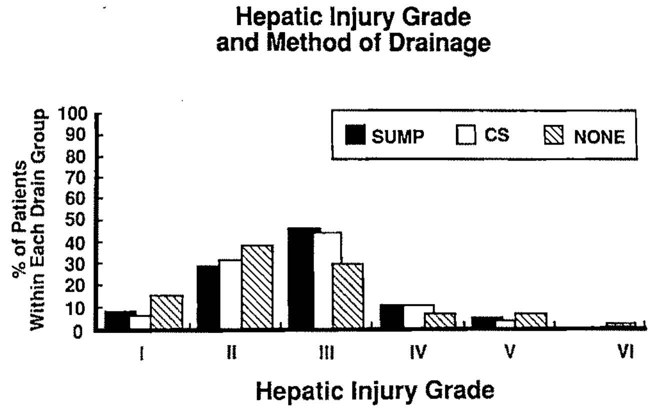

FIG. 3. Distribution of drainage groups according to hepatic injury grade.

There were no differences among the groups, with the exception of greater transfusions in the closed suction group ($p < 0.03$).

The outcomes of drainage were measured by bile leaks on HIDA scan, development of perihepatic abscess, and length of hospitalization. Table 3 summarizes those results. Sump drains were associated with a significantly greater number of bile leaks compared to either closed suction or no drainage ($p < 0.01$). Two patients had biliary cutaneous fistulae that eventually closed; initially one had sump drainage and the other received no drain. When evaluating the incidence of perihepatic abscess, sump drains again were found to have a significantly higher rate than closed suction ($p < 0.03$), and a twofold incidence compared to no drainage, although the latter was not statistically significant ($p < 0.1$). Table 4 illustrates the abscesses in the drain groups according to the hepatic injury scale and mechanism of injury. Although the gastrointestinal tract frequently is implicated as the source for bacterial colonization and subsequent infection after traumatic injury, microbiologic evaluation of the perihepatic abscesses revealed that 68% of the bacterial isolates associated with sump drainage had no hollow viscus injury (compared to 30% associated with no drainage ($p < 0.005$) and 0% with closed suction drainage ($p < 0.001$).

The length of hospitalization also was significantly greater for sump drainage patients compared with the

TABLE 3. *Outcome Measurements and Drainage*

Drainage	Perihepatic Abscess*	Bile Leak†	Length of Hospitalization‡
Closed suction	3.5%	19%	13.5 days
Sump	13.0%	41%	18.0 days
No drain	6.7%	23%	13.5 days

* $p < 0.03$ sump *vs.* closed suction.
† $p < 0.01$ sump *vs.* closed suction or no drain.
‡ $p < 0.03$ sump *vs.* closed suction or no drain.

TABLE 4. *Occurence of Perihepatic Abscess According to Hepatic Injury Grade and Mechanism of Injury*

	Hepatic Injury Grade						Mechanism of Injury
Drainage	I	II	III	IV	V	VI	Blunt/ Penetrating
Closed suction (4)		1	2	1			1/3
Sump (13)	1	2	6	3	1		6/7
No drain (17)		7	6	2	1	1	8/9
Total (34)	1	10	14	6	2	1	15/19

other two groups ($p < 0.03$). Although this was accounted for partially by the increased hospitalization engendered by the complications in those patients, sump drainage also was associated with greater lengths of stay in patients without complications compared to the other groups ($p < 0.01$). This increased stay appears to be the result of extending the hospitalization to back out the drain gradually.

Risk Factor Analysis

This was undertaken to determine those clinical parameters that were associated with the development of perihepatic abscesses. Univariate analysis was performed for the impact of age, ISS, ATI, mechanism of injury, admission blood pressure, liver injury grade, presence of hollow viscus injury, and transfusions. The results of that analysis are listed in Table 5. Those found to be significant included ATI, transfusions, and hollow viscus injury, in that order of significance. A multivariate analysis, in which method of drainage was also added, then was undertaken to evaluate independent significance of those risk factors. Increasing ATI and transfusions were found to be significant factors. Similarly sump drainage was associated independently with development of perihepatic abscesses. Closed suction drainage was a protective factor against abscess development.

Deaths

There were 27 deaths (5.6%). Thirteen of those were not liver related; in the remaining 14 deaths, the liver injury was a contributory factor. The mechanisms of injury in the deaths were blunt in 20 (74%) and penetrating in seven (26%). Thus the overall mortality rate for the entire population associated with penetrating wounds was 2% compared to 12% for blunt injuries. Eight of the 13 non–liver-related deaths were due primarily to closed head injury, 3 were due to sepsis and multiple-organ failure, 1 was due to associated major vascular injury, and 1 was due to pulmonary thromboembolism. Of the 14 deaths directly related to liver injury, 5 had grade III injuries, 4 had grade IV, 3 had grade V, and 2 had grade VI. Six of the liver-related deaths occurred within 2 days of admission due to hemorrhagic shock and coagulopathy, 6 occurred with sepsis and multiple-organ failure, and 2 died with hepatic artery pseudoaneurysm and hemobilia. Three of the eight deaths from sepsis occurred in sump-drained injuries and the source of sepsis was the perihepatic abscess.

Hemobilia

Six patients developed hemobilia after liver injury, representing an incidence of 1.2%. All were associated with hepatic artery pseudoaneurysms occurring in branches of the main arteries. Presentation with upper gastrointestinal hemorrhage occurred 1 to 8 weeks after injury (average, 3 weeks). Three hemorrhages resulted from penetrating injury and three from blunt. Five patients with large false aneurysm cavities were managed by formal hepatic resection; one with a small pseudoaneurysm had radiographic embolization. One patient died in the operating room and one died in the immediate postoperative period. The patient who died in the operating room was septic from a large infected pseudoaneurysm; inability to control the porta hepatis due to severe inflammation resulted in exsanguination during resection. The other patient who died had massive upper gastrointestinal hemorrhage and also died primarily due to inability to control the porta hepatis.

Discussion

The morbidity and mortality rates associated with liver injuries vary significantly depending on the mechanism of injury. Recent reports of liver injuries demonstrate disparate mortality rates ranging from 1.2% to 31%.[5,9-11] Those with low rates generally result from a preponderance of patients sustaining penetrating wounds (1.2% and 10.5%).[5,9] Higher mortality rates are reported when the experience is heavily weighted with blunt injury (29% and 31%).[10,11] Our institutional experience illustrated that point with a 2% mortality rate from penetrating wounds and a 12% rate from blunt trauma. Blunt injury accounted for 35% of the population, but 74% of the deaths. Death from penetrating wounds is generally in two phases: early

TABLE 5. *Univariate Analysis of Risk Factors for Perihepatic Abscess*

Variable (mean)	Perihepatic Abscess	No Perihepatic Abscess	p Value
ATI	22	15	0.002
Transfusion (units)	8.2	4.8	0.05
Hollow viscus injury	38%	20%	0.05
Hepatic injury score	3.03	2.63	NS
ISS (blunt)	35	32	NS

ATI, Abdominal Trauma Index; ISS, Injury Severity Score; NS, not significant.

deaths from hemorrhage and hypovolemic shock from either the liver or associated major vascular injuries, and late deaths from sepsis and multiple-organ failure.[2,12] Death associated with blunt injury also occurs in early and late phases, but the causative factors differ from penetrating trauma. Although early deaths occur from hemorrhage associated with major liver fracture, a substantial number of these multiply injured patients die from brain injury. The late phase of deaths from blunt injury similarly is twofold: closed head injury and sepsis with multiple-organ failure. One half of the deaths in this report were not liver related and one half were associated with the hepatic injury. While closed head injury was responsible for 60% of the non–liver-related deaths, equal numbers of liver injury-related deaths were due to hemorrhage and sepsis, regardless of mechanism of injury. Indeed efforts to reduce liver injury-related morbidity must be directed at expeditious hemostasis and to reducing infectious complications.

In the course of the 20th century, much progress has been made in achieving hepatic injury hemostasis. However the progress has not always been linear. Some lessons have been learned, set aside, and then reconsidered in light of changing circumstances. In the beginning of this century, innovative surgeons successfully applied various packing techniques for the control of traumatic liver bleeding.[13,14] Packing and mass suture techniques were applied widely through World War I and into World War II.[15] Mortality rates for liver injuries were about 60% at that time.[16] Assessment of the experience with liver injuries sustained during World War II, in which a 28% liver injury mortality rate was noted, led Madding[17] to recommend avoidance of liver packing because of secondary hemorrhage, sepsis, and hemobilia. At that time the general approach to packing was to place a long nonabsorbable cloth pack into the area of injury and withdraw it through drain incisions without a second laparotomy.

In the past decade, there has been a return to nonabsorbable packing.[18–20] Although one of those reports again condemned the technique,[18] others have been satisfied with the results in a select group of patients with severe injuries.[19,20] Generally it has been used in patients who have shattering liver injuries, when after major vessels have been ligated, continued diffuse bleeding occurs that is associated with hypothermia, acidosis, and concomitant coagulopathy. This is a small group, representing approximately 2% to 4% in the reports. Mortality rates of 10%,[20] 17%,[19] and 57%[18] have been observed, with respective intra-abdominal sepsis rates of 0%, 40%, and 83%. We have used gauze packing when omentum was either unavailable or ineffective. Gauze packing provided satisfactory results with a mortality rate of 29% and a perihepatic abscess rate of 30% in the series. The gauze packs are removed after correction of metabolic and hematologic abnormalities, usually 24 hours after initial packing. Early removal of the foreign body is important in minimizing infection.

Fortunately most liver injuries (70% to 90%) require minor therapy.[9,21,22] During the past 20 years, various approaches have been advocated for the 10% to 30% of major injuries. Formal hepatic resection enjoyed brief support but has been fairly uniformly decried.[23] Hepatic artery ligation and atriocaval shunting were introduced with significant enthusiasm.[24–26] However, over time, subsequent clinical investigations dampened enthusiasm for any widespread application.[21,27] Both techniques sometimes may be practical: hepatic ligation for inaccessible hepatic artery bleeding or extensive dissecting subcapsular hematomas with arteriolar bleed, or atriocaval shunting for true retrohepatic vena cava injuries.

We believe omental packing offers the most effective treatment for most major hepatic injuries. Stone and Lamb[28] first described the technique and demonstrated excellent clinical results. The requirement for expedient control of liver bleeding is satisfied by this technically simple approach. It is, in essence, a rediscovery of the principles of tamponade introduced by Pringle[13] and Schroeder[14] in the early 1900s. However omentum offers the distinct advantages of being autogenous and viable, and thus does not require removal and minimizes sepsis. The technique is most helpful for grades III to V injuries with stellate fractures and deep cracks, and most are due to blunt injury, which generally results in hepatic venous bleeding rather than arterial bleeding.[29] Tamponade is well effected by omentum in the low-pressure venous system. Omental packing was applied in 60% of our major injuries, yielding a mortality rate of 7% and an abscess rate of 8%.

With many techniques available for major liver injury management, it is obvious that the surgeon must tailor the surgical approach to the individual injury. A familiarity with the indications, limitations, and applications of the various approaches should be developed. Newer approaches are being investigated that eventually will modify current approaches. Fibrin glue, laparoscopy, and liver transplantation all have been reported.[30–32]

After hemorrhage sepsis remains the major factor for liver-related morbidity. Eliminating the early deaths in this series yielded a perihepatic abscess rate of 7.2%. Intra-abdominal abscesses have been noted to account for 25% of late deaths[2] and were responsible for 27% of the deaths in this report. Several factors have been reported to be associated with sepsis. Shock has been noted to produce a threefold increase in abdominal abscess after liver injury.[1] This was not observed in the present study. However increasing transfusion requirements were observed to be the most significant factor associated with perihepatic abscess in this multivariate analysis. Scott et al.[3] also performed a multivariate analysis for risk of intra-abdominal sepsis following hepatic trauma and similarly found transfusions to be a highly significant ($p < 0.0001$) risk factor. While Noyes et al.[1] noted the aforementioned threefold increase with shock, they noted a 10-fold increased risk when more than six units of blood were transfused. Transfusion requirements correlate primarily because they are a more sensitive indicator of significant hypovolemic shock than are isolated measures of blood pressure. In addition hemoglobin has been experimentally demonstrated to be a potent adjuvant factor for the production of infection.[33] Impairment of cell-mediated immunity and stimulation of suppression T cells also have been correlated with blood transfusion.[34,35]

Blunt injury produces more deaths than penetrating injury in essentially all series. This is mostly influenced by the greater magnitude of associated injury. Our results also noted significantly higher blunt mortality but the incidence of perihepatic sepsis was only slightly greater for blunt patients (9% compared to 6%). Mechanism of injury was not found to be a risk for sepsis in either this multivariate analysis or in that of Scott et al.[3] Similarly ISS (applied only for blunt injuries) was not associated with increased septic complications. Bacterial contamination from gastrointestinal injury might be assumed to be significantly associated with abscess following liver injury. This has not been observed. Although hollow viscus injury was significant in our univariate analysis, no significance was found with multivariate analysis.

Severity, frequency, and type of associated injuries, as well as severity of the liver injury itself, have been studied with respect to hepatic sepsis. Three or more associated abdominal organ injuries have been associated with a threefold increase of intra-abdominal abscess.[1] Although we could not correlate ISS, a measure of total body injury, with perihepatic abscess, evaluation of only associated abdominal injuries by the ATI demonstrated independent significance with multivariate analysis. The severity of liver injury has been demonstrated by Flint et al.[4] to correlate with an increasing rate of sepsis. This also was noted in this report when correlating the frequency of perihepatic abscess with hepatic injury grade (Fig. 2). However statistical significance was not obtained, probably due to relatively small numbers with the advanced injuries.

There were three variables noted to be independently associated with perihepatic sepsis: ATI, transfusion requirements, and sump drainage. The surgeon has no control over the severity of associated abdominal injuries, but very importantly, has considerable control over the other two variables. Prompt, expeditious, and appropriate operative management of liver injuries will reduce perioperative blood loss with a diminution in transfusion requirements and a consonant reduction in abscess formation. That area of clinical management of liver injuries remains a major challenge to the surgeon, but eliminating sump drainage as a variable presents no challenge.

The rationale for drainage of liver injuries is to evacuate blood and bile that may accumulate in the right upper quadrant. The reports by Madding[17] of the World War II experience securely entrenched the use of wide drainage to prevent perihepatic collections and infections. It has been noted that those conclusions were not supported by the available data.[7] A decade after World War II, both Sparkman[36] and Mikeskey[37] noted a lower incidence of peritoneal sepsis in undrained patients, although the undrained patients generally were less severely injured. Fisher et al.[7] in 1977 reported on 254 patients, 27 of whom had peritoneal drainage. Intra-abdominal sepsis occurred in 4.8% of the undrained and 7.4% of the drained patients. They threw down the gauntlet, proclaiming that 'peritoneal drainage is not indicated for capsular tears or for minor or major liver lacerations, and that the value of peritoneal drainage in the prevention of intra-abdominal sepsis following bursting liver injuries remains unsubstantiated.'[7] Although retrospective and nonrandomized, the results of that report are impressive.

Mullins et al.[5] reported the first prospective randomized trial of drainage in liver trauma. After excluding six patients who were noted to have small bile leaks at the time of surgery, 161 patients were randomized to Penrose drain (*versus* no drain). An 8% liver-related complication rate resulted that was the same for both groups. The results again were impressive, but 96% of the patients sustained penetrating wounds and severity of injury was not stratified. In a small prospective study of 56 patients, Gillmore et al.[6] prospectively randomized patients to no drain (*versus* to closed suction). They noted 4.2% and 3.1% intra-abdominal abscess rates, respectively, for closed suction and no drain. They concluded that open drainage should not be used. There has been a growing consensus that drainage is not necessary for mild injuries (grades I and II).[2] However a recent multicenter study reported that 94% of 210 complex liver injuries were drained routinely. It was recently stated, 'Use of a closed system in the most severe injuries is still controversial and needs to be addressed in a prospective trial.'[2]

The present drainage study was initiated to address the place for both sump and closed suction drainage. Sump drainage had not been prospectively evaluated, but we believe it is commonly applied across the country. Sump drainage produced significantly greater sepsis rates than the other methods and 3 of 13 failures resulted in death. The data appears clear: sump drainage is hazardous and should be abandoned. The probable reason for failure of sump drainage is bacterial colonization of the area. This observation of colonization mirrors our results with the failure of sump drainage for pancreatic injuries.[38] It might be criticized that the sump drains were poorly handled and the technique of withdrawal precipitated failures. There are undoubtedly many approaches used in care and removal of sump drains, but we doubt that they alter colonization significantly. The HIDA scans were performed in this study specifically to follow bile leaks in the three groups. The leak rate was significantly higher with sump drainage. The reasons are not clear to us. Perhaps in some way colonization promotes bile leak. Although abscesses were found to occur more frequently when a leak was demonstrated, 80% of the leaks were inconsequential. These results with HIDA scan are very similar to those reported by Gartman et al.[39] in a group of 26 patients following complex liver trauma. HIDA scanning should not be used routinely following injury, but sometimes may be beneficial in workup of the patient with liver injury with right upper quadrant pain in the postoperative period. However CT scans generally offer more pertinent information.

Is there any difference between closed suction and no drainage regardless of liver injury severity? Our data demonstrated a slightly higher incidence of perihepatic abscess with no drainage: 6.7% compared to 3.5%. This was not significant. A power analysis was done and with an $\alpha = 0.05$ and $1\text{-}\beta = 0.8$, we would require 650 patients in each group to demonstrate significance if the current rates continued. With our present patient volume, 12 years would be required to obtain such data. Perhaps a well-controlled multi-institutional trial is warranted. Until further data are available, closed suction drainage is appropriate.

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DISCUSSIONS

DR. HARLAN STONE (Cleveland, Ohio): I highly recommend to the membership the practical algorithm for management of liver injuries as given in this paper. It is easily applied and it has a proved, excellent track record. However the major issue to me in this presentation was drainage of the liver wound—how and when it is done.

Clearly with minor injuries with no obvious bowel leak, it is not necessary. But the identification of those is indeed required.

We all recognize that the drain is a foreign body and it prevents healing along a prescribed route. Our goal is that all undesirable matter should have a speedy and direct exit. Such flow to the outside depends on the viscosity of the fluid, the amount of particulate matter within, and the differentials in pressure between the intra-abdominal space and the outside.

The Penrose drain has failed, primarily because it merely effects an escape of overflow, and it is very subject to contamination. Accordingly we rely on some form of suction or dependency. I do not believe God had the surgeon in mind when He created the abdomen, because we operate from the front, but for dependency we would need a posterior route. Therefore we rely on the sump.

The sump creates a sufficient difference in pressure to guarantee a reliable flow. But it is at a price, and the price is the influx of air from without. And in that air are, presumably, hospital pathogens.

Thus we must choose some form of closed-suction drainage such as Dr. Fabian described. It establishes a relatively efficient evacuation system in concert, though, with the absence of intake of unwanted pathogens from the immediate hospital environment.

I would refer you to page 15 of his manuscript, where it states, "Although the gastrointestinal tract is frequently implicated as the source for bacterial colonization and subsequent infection following traumatic injury, evaluation of the perihepatic abscesses reveal that 68% with sump drainage had no hollow viscous injury, as compared to 0% for those with closed suction drainage." This yields a probability value of 0.001.

So clearly closed suction drainage is the system of choice. But as you note, Tim, and you do so nicely, we must all remember that the drain truly can be a two-edged sword. There is no micro traffic cop along the drain tract that keeps everything evil out. We must realize, then, that no matter how perfect the drainage system is, it still can lead to an unwanted result.

DR. TIMOTHY FABIAN (Closing discussion): To put it into perspective relative to other work on drainage in the past, after World War II, it was accepted, based on Madding's report, that wide drainage was certainly preferred. And this, again, was adopted similar to the reason that colon injury management was adopted as previously discussed this morning.

However there was an interesting paper that came out of St. Paul Ramsey by Drs. Fischer and Perry in 1978, in which 90% of their patients had no drainage. They threw down the gauntlet at that time, saying that "You can't improve on our results." The results are impressive, and I would recommend that the audience look at that manuscript.

However the first prospective trial of drainage was done again by Dr. Stone, who has done so many of the first prospective trials in surgery. He looked at Penrose *versus* no drainage and found, again, that Penrose drains were bad.

The next prospective trial was done by the Tulane service at Charity Hospital and found that closed suction was, indeed, preferable to no drainage. But, like ours, there were no statistically significant differences.

The practitioner must ask himself if the infection rate, although low with this series, is significant? I think you could take our data and justify no drainage with all injuries, actually. It's 3.5% compared to 6.7%, twice as many patients but actually only 3% more. We did a power analysis to evaluate how many cases it would take to prove that there was a difference, assuming these trends continued with a power of 0.8 and confidence levels of 95%, it would have taken 650 patients in each group, which would take us 12 years to do. And, although it was interesting to me, it's not that interesting.

So, again, we are basing our present management on the fact that there were lower abscess rates with closed suction drainage and on the fact that there really are no side effects or complications associated with the soft rubber drain and would recommend it for your consideration in the future.

A Circulating Factor(s) Mediates Cell Depolarization in Hemorrhagic Shock

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Cell depolarization in hemorrhagic shock has been attributed to hypoperfusion, but the mechanism remains unclear. Suspensions of single cell lines loaded with the potential-sensitive fluorescent dye bis-(1,3-dibutylbarbiturioc acid) trimethine oxonal (DIBAC) and exposed for 30 minutes to rat plasma drawn either before or after hemorrhagic shock (bled 20 mL/kg: mean arterial blood pressure less than 40 mmHg) were studied. Plasma drawn after, but not before, hemorrhage led to partial depolarization regardless of cell type (rat H9C2 skeletal muscle, A-10 smooth muscle, C-9 liver, adrenal, kidney, red blood cell [RBC], white blood cell [WBC]) or species (cat, dog, pig RBC; cat WBC; mouse C2C12 skeletal muscle; and human intestinal smooth muscle [HISM]). Dialysis did not remove the factor(s), suggesting a molecular weight of more than 10,000 daltons. The factor appeared within 5 minutes of shock. The depolarization amplitude increased as a function of plasma concentration and demonstrated saturation kinetics indicating specific receptor binding. Cells were equivalently oxygenated, excluding hypoperfusion as a necessary condition for depolarization. Tumor necrosis factor or platelet activating factor alone or in combination were not effective in this system. Stable measurements can be obtained with this noninvasive system that avoids cell injury consequent to cell impalement with electrodes. This system provides a sensitive *in vitro* bioassay that should permit identification of the plasma factors mediating cell depolarization, as well as definition of the responsible intracellular mechanisms.

THE PATHOPHYSIOLOGY OF hypovolemic and septic shock is characterized by cell membrane depolarization, that is, a decrease in the absolute value of the transmembrane potential. It has been suggested that the membrane depolarization results from hypoxia, which results, in turn, from hypoperfusion of tissue.[1] Several authors noted the presence of toxic factors that appear after hemorrhage,[2-6] but none have been identified. Studies that applied tourniquet isolation[7] or cross-perfusion[8] suggested the presence of circulating factors mediating depolarization of muscle cells *in vivo*. The use of microelectrodes for recording membrane potential in these and related studies[7,8] has been criticized because of artifacts that may result from puncture of cells.

In the present report we developed a bioassay for a presumptive circulating factor(s) based on the sensitivity of the fluorescence of the membrane dye bis-(1,3-dibutylbarbiturio acid) trimethine oxonal (DIBAC, Molecular Probes, Eugene, OR) to changes in the resting membrane potential and the ability to manipulate such changes by exposure of cells to plasma obtained from rats in shock. This measurement of changes in fluorescence of a membrane-bound dye avoids the problems associated with direct puncture of cells. We used this method to demonstrate the presence of a high–molecular-weight substance(s) that appears in plasma rapidly after hemorrhage and that depolarizes cells derived from many tissues and species, including humans.

Methods

Tissues and Cells

Red blood cells (RBC) were prepared from whole blood by low-speed centrifugation. The RBCs were washed free of residual plasma by centrifugation and 50 uL packed RBCs were resuspended in 5 mL RBC washing solution consisting of 150 mmol/L (millimolar) NaCl; 1 mmol/L $MgCl2$; 10 mmol/L TRIS-HCI, pH 7.4; 0.1 mmol/L ethylene glycol-bis (β-aminoethyl ether) N,N,N',N'-tetraacetic acid (EGTA); and 14 mmol/L glucose.[9] White blood cells (WBC) were prepared by differential centrifugation of the

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'buffy coat' from RBC preparations. For some experiments WBCs were purified further by centrifugation through Lymphocyte Separation Medium (Organon Teknika, Durham, NC). Defined cell lines derived from tissue culture were obtained from American Type Culture Collection (Rockville, MD) and were maintained in culture. Rat kidney and adrenal tissue were harvested 2 hours after hemorrhage (described below) or from nonhemorrhaged controls. The tissue was dissociated with collagenase and the epithelial cells were harvested and cultured according to the method of Engeland et al.[10] Dog adipose tissue was dissociated with collagenase and the adipocytes were cultured under the same conditions used for the kidney and adrenal tissues.

Preparation of Rats and Plasma

Male Sprague-Dawley rats, weighing 300 to 400 g, were anesthetized with pentobarbital-sodium (50 mg/kg, administered intraperitoneally) and femoral venous and arterial cannulae (PE-50, Dural Plastics, Dural, NSW, Australia) were placed using sterile procedures previously described.[11,12] Cannulae were tunneled under the skin of the back and brought out through a flexible stainless steel spring attached to the back of the neck. The free end of the spring was attached to the top of the cage and was allowed to rotate freely. Incisions were filled with xylocaine jelly and Bacitracin (Medalist, San Francisco, CA) to desensitize the surgical area and prevent infection, respectively. All rats recovered and were caged singly in a controlled temperature environment. The light cycle was 12 hours of light and 12 hours of dark. All rats had access to food and water *ad libitum*. Cannulae were flushed daily 1 to 3 hours after the beginning of the photoperiod. Hemorrhage was induced (20 mL/kg for 4 minutes) from the arterial cannula in the morning, 1 or 2 hours after lights were turned on. Blood samples (0.5 to 1.0 mL) were drawn over heparin at times 0, 2, 3, 10, 20, 30, 60, 120 minutes after hemorrhage. In some experiments, blood samples were also taken at 15, 30, 60, 90, 150, and 210 seconds. Blood samples taken between 0 and 4 minutes were derived from the hemorrhage volume. Blood samples were centrifuged and the plasma was removed and put on ice. Rats were killed after 2 hours by overdose of pentobarbital (100 mg/kg). Plasma was assayed on the day of collection. These experimental protocols were approved by the Committee on Animal Care and Use at the University of Maryland, Baltimore, MD.

Fluorescence Assay of Membrane Potential

Bis- (1,3-dibutylbarbituric acid) trimethine oxonol is a member of the oxonol class of membrane dyes in which a negative charge is delocalized over a generally planer molecule. Oxonol dyes behave much like tetraphenyl boron and triphenylmethyl phosphonium ions and partition into hydrophobic regions of membranes with consequent fluorescence enhancement.[13] This tendency to partition from the extracellular medium into the membrane is countered by the magnitude of the negative interior of the cells, thus providing a means to measure the relative cell polarity.

Except as noted, RBCs and WBCs were incubated and observed in Na/K buffer consisting of 125 mmol/L NaCl; 5 KCl; 23 mmol/L NaHCO3; 0.8 mmol/L MgCl2, 1.8 mmol/L CaCl2; and 20 mmol/L HEPES, pH 7.4. Red blood cells (50 μL) were mixed with 50 μL plasma or buffer and 100 μL buffer containing 300 nmol/l (nanomolar) DIBAC and incubated for 30 minutes at room temperature. Red blood cells were washed free of plasma by addition of 1.5 mL buffer containing 150 nmol/L DIBAC and pelleted in an Eppendorf centrifuge. The cells were resuspended in 3.0 mL buffer with 150 nmol/L DIBAC and the fluorescence was measured in counts per second(cps) using a Spex Industries (Edison, NJ) ARCM Cation Measurement spectrofluorometer. Specimens were excited by a 150-watt xenon lamp filtered to a 10-nm band width about 490 nm by a Corion P10-490-F-F519 filter; emission was observed through a 10-nm band width about 510 nm *via* a P10-510-F-P558 filter (Corion Corp., Holliston, MA). Other cell types were counted with trypan blue and suspended in RBC washing solution such that 50 μL contained approximately 500,000 cells. The remainder of the procedure was similar to that for RBCs, except for a lower *g*-force centrifugation (half speed IEC model UV centrifuge) was used to wash cells free of plasma. For some experiments cells were washed by layering over 2 mL of 10% Hypaque (Winthrop Labs, New York, NY) in Na/K buffer containing 150 nmol/L DIBAC and centrifuging at low speed. We observed approximately a 1% increase in the fluorescence amplitude per millivolt depolarization, which is consistent with published observations.[14]

Reagents

Platelet activating factor (PAF) was obtained from Calbiochem (La Jolla, CA). Human tumor necrosis factor(alpha) (TNF) and endothelins 1, 2, and 3 were obtained from Bachem (Torrance, CA). High-performance liquid chromatography (HPLC) grade water from a RGW-5 system (Photronix Corp., Medway, MA) was used in all solutions. All other reagent, and chemicals were obtained from Sigma Chemical Co. (St. Louis, MO).

Results

Shires and associates[1] previously showed that hemorrhage leads to a depolarization of muscle cells *in vivo* as measured by microelectrodes. To determine if hemorrhage will depolarize cultured cells in an *in vitro* system using the fluorescent dye, DIBAC, we challenged renal epithelial cells (derived from renal tissue that was removed 2 hours after hemorrhage) with plasma taken before and 2 hours after hemorrhage (control and shock plasma). In a single experiment, we found that the fluorescence intensities were 21,500 and 57,100 cps for control and shock plasma, respectively. The ratio of intensities was 2.65. We also found that the renal epithelial cells derived from nonhemorrhaged rats also responded to control and shock plasma (12,500 and 57,100 cps, respectively, for a single experiment; the ratio of intensities was 3.40), thereby demonstrating that the tissue need not be exposed to shock before harvesting to show depolarization when incubated with shock plasma.

To determine if the difference in fluorescence intensity between cells exposed to control and shock plasma results from a differential retention of plasma protein, renal epithelial cells were incubated with plasma, washed, and resuspended in fresh buffer. Under these conditions, we found that the fluorescence intensity from cells exposed to control plasma or shock plasma was 93,900 and 145,300 cps, respectively (in a single experiment), suggesting that the difference in intensity does not result from retention of plasma. However, because the intensity ratio (1.55) was found to be smaller than those in the two previous experiments, these results also suggest that plasma proteins artifactually enhance fluorescence if not removed by washing. Because of these findings, all subsequent experiments were performed after washing cells free of any residual plasma. Cells not derived from cultured cell lines were obtained from control (nonhemorrhaged) rats.

Species and Cell Type Specificity and Ionic Composition of Buffer

Plasma taken 1 hour after hemorrhage depolarized RBCs from rat, cat, dog, and pig (Table 1) smooth and skeletal muscle, liver, kidney, and adrenal from rat; dog adipocytes; mouse skeletal; and human intestinal smooth muscle (Table 2). We also found that dog and pig RBCs depolarized to shock plasma only when washed and incubated in a high Na^+ buffer (Table 1). Substitution of K^+ for Na^+ prevented depolarization (Table 1), suggesting that Na^+ ions are essential. Depolarization occurred when the hydrogen ion concentration of the buffer was adjusted to pH 7.4, suggesting that acidosis is not necessary for depolarization by shock plasma.

TABLE 1. *Red Blood Cell Response to Shock Plasma*

Species	Ratio
Rat	1.20
Cat	1.24
Dog	1.68
Dog	1.03(*)
Pig	1.80
Pig	1.08(*)

Incubation and observation was in sodium buffer (mmol/L [millimolar]): 125 NaCl; 23 NaHCO3; 0.8 MgCl2; 1.8 CaCl2; 1 NaH2PO4; 20 HEPES pH 7.4), except as noted (*), which was in potassium buffer, in which KCl was substituted for NaCl. Ratio is fluorescence intensity after exposure to shock plasma divided by that after control plasma.

TABLE 2. *Response to Shock Plasma*

Cell Type	Ratio
Rat adrenal	1.11
R. a7r5 smooth	1.40
R. C-9 liver	1.15
R. H9C2 skeletal	1.30
R. A-10 aortic	1.40
R. WBC	1.52
Mouse C2C12 skeletal	1.17
HISM	1.12
Cat WBC	1.19(*)
Dog adipocyte	1.46

Conditions were as given in Methods using Na/K buffer, except (*) used sodium buffer as in Table 1.

WBC, white blood cell; HISM, human intestinal smooth muscle.

Time Course of Appearance of the Factor(s)

Plasma taken at various times after 20 mL/kg (for 4 minutes) hemorrhage causes depolarization of rat RBCs and rat a7r5 smooth muscle cells that reaches a maximum at approximately 20 minutes followed by a gradual decline (Fig. 1). The ordinate is expressed as the percentage change in fluorescence intensity because this parameter is linear with change in resting membrane potential.[14] The response determined with a7r5 smooth muscle cells is similar to the response of RBCs. However the effect persists longer than it does in RBCs.

Dose Response

The fluorescence amplitude caused by depolarization of rat RBCs increases with plasma concentration and then saturates, indicating an equilibrium binding process (Fig. 2). Equilibrium kinetics suggest a receptor-mediated process.

Cytokines

Because of reports that TNFα depolarizes skeletal muscle *in vitro*,[15] and that PAF causes membrane depolarization *in vivo*,[16] we tested these factors in our assay. Whereas plasma from hemorrhaged rats depolarized rat WBCs, neither 0.07 μmol/L (micromolar) TNFα, 7 μmol/L PAF-18, or a mixture of 0.05 μmol/L TNFα plus 5 μmol/L PAF-18 depolarized rat WBCs (Fig. 3). These same substances as well as heparin (tested because it was used in the collection of whole blood) did not depolarize

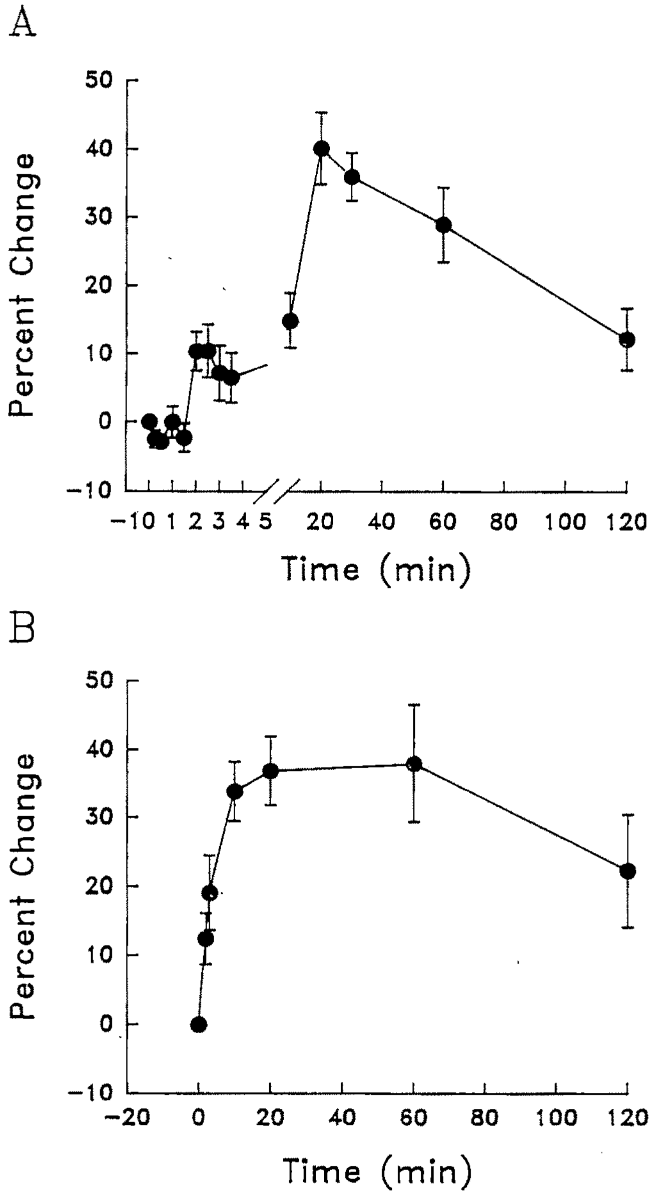

FIG. 1A and B. Appearance of factor in rat plasma using rat red blood cells (A) and the cultured cell line, a7r5 (B). At the indicated times, 0.5 mL of blood was drawn from cannulated rats and plasma was prepared as given in Methods. Red blood cells were diluted such that in the absence of plasma, when ultimately diluted to 3.0 mL for fluorometric determination, 50 μL would yield a fluorescence intensity of 25,000 to 35,000 cps or about 10%–15% of the maximum experimentally observed fluorescence amplitude. The remainder of the procedure is given in Methods. The ordinate is expressed as a percentage change relative to the intensity produced by incubation with plasma drawn in the first 0.5 mL of blood. Symbols indicate means and standard errors (n = 13).

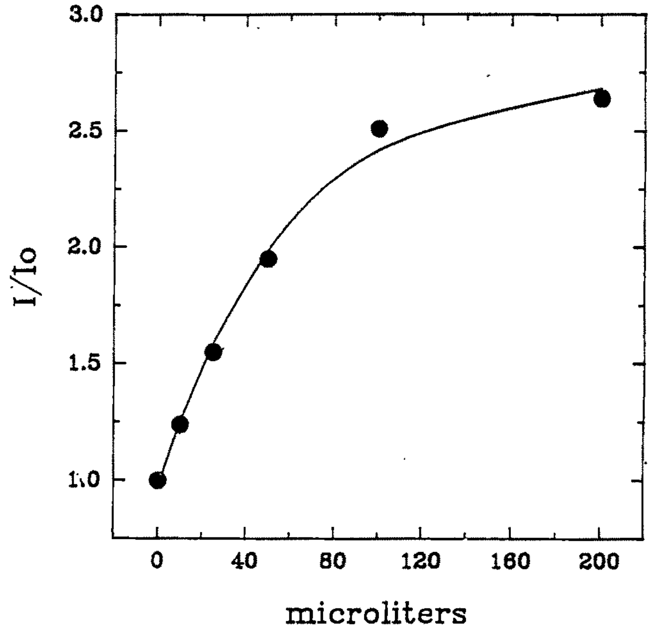

FIG. 2. Titration of RBCs with rat plasma Rat. Red blood cells (50 μL), the indicated volumes of plasma (drawn 60 minutes after hemorrhage), and buffer sufficient to bring the total to 400 μL were mixed and incubated for 15 minutes, then were washed as given in Methods. Symbols are averages of four determinations.

rat RBCs (Table 3). To eliminate the possibility that some plasma factor might be required for TNFα activity to become manifest, we incubated rat A-10 smooth muscle cells with control plasma and concentrations of TNFα ranging from 50 ng to 50 pg/mL[15] without observing depolarization (Fig. 4). Finally, to identify any contribution of TNFα to cellular depolarization, we incubated shock plasma with monoclonal anti-TNFα antibody (provided by Dr. Kevin J. Tracey, Cornell University Medical College) sufficient to yield a 100-fold molar excess, assuming a plasma concentration of 50 ng/mL TNFα. We observed no blockade of depolarization (Fig. 5). The report that TNFα depolarized excised rat muscle *in vitro*[15] suggested

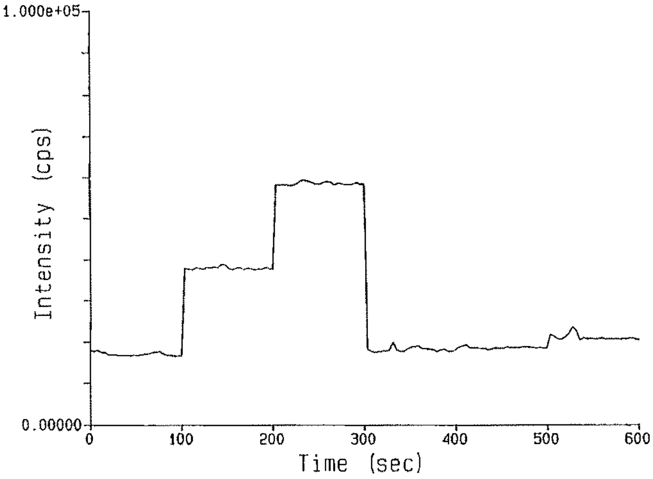

FIG. 3. Effect of TNF and PAF on rat WBCs. Rat WBCs were incubated as given in Methods and separate cuvettes were observed for 100 seconds starting at the indicated times. 0 Sec: Na/K buffer; 100 Sec: control plasma; 200 Sec: shock plasma; 300 Sec: 0.07 μmol/L human TNFα; 400 Sec: 7 μmol/L PAF; 500 Sec: 0.07 μmol/L TNF + 7 μmol/L PAF.

TABLE 3. *Effect of TNF and Heparin on Dog RBCS*

Incubation	Intensity	Intensity
Buffer	30,700	25,700
TNF	26,400	25,000
Heparin	29,300	25,000

Tumor necrosis factor (TNF) 5000 units (0.035 μmol/L [micromolar]); heparin 40 units (200 units/mL).

the possibility that TNFα might stimulate the release of endothelin from the blood vessels contained within the preparation. Therefore we tested endothelins 1, 2, and 3. None of the endothelins (0.1 μmol/L) depolarized rat RBCs (Table 4); however they had varying effects on the smooth muscle lines. Endothelin 3 but not 1 or 2 depolarized human intestinal smooth muscle (HISM), whereas endothelins 1 and 2 but not 3 depolarized rat A-10 aortic smooth muscle (Table 4).

Discussion

Shires and associates[1] identified depolarization of cellular membranes as the primary initial change in hemorrhagic shock. This inference was made from analysis of intracellular microelectrode measurements *in vivo* that show that the resting membrane electrical potential of skeletal muscle increases from −90 mV in normal tissues to −70 mV in tissues in shocked animals. This defect was confirmed by tissue analysis, which demonstrated increased intracellular water content, sodium and chloride concentrations, as well as decreased intracellular potassium concentration.[17–19] Trunkey et al.[8] used microelectrodes to measure a 20-mV increase in the resting potential of skeletal muscle of a cross-perfused baboon, again suggesting a circulating factor. However this observation was not pursued further. Similar alterations in membrane functioning of RBCs were shown to accompany septic shock,[20] an observation that Gann[21] interpreted to imply the existence of a circulating factor responsible for the defect. The altered intracellular concentration of these ions suffices to account for the altered resting membrane potential as calculated by the Nernst equation.[22] Use of microelectrodes has been criticized because of several potential artifacts, including direct cellular injury resulting from puncture, unstable recording, leakage of ions around electrode, and leaching of ions from electrode.[14,23]

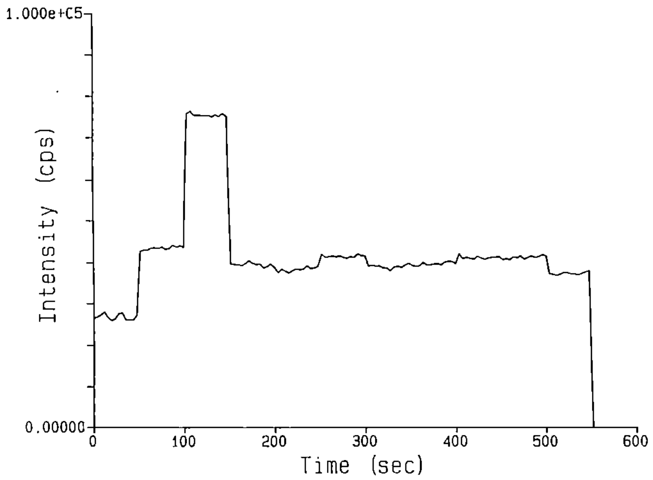

FIG. 4. Titration of A-10 cells with TNFα/control plasma. Rat aortic smooth muscle A-10 cells were incubated with control plasma and the indicated concentrations of TNF-α, washed, and fluorescence measured. Reaction mixtures were observed in separate cuvettes starting at the indicated times. All incubations with TNFα contained the same concentration of control plasma as did the sample assayed at 50 Sec. 0 Sec: buffer; 50 Sec: control plasma; 100 Sec: shock plasma; 150 Sec: 50 ng/mL; 200 Sec: 10 ng/mL; 250 Sec: 5 ng/ml; 300 Sec: 1 ng/mL; 350 Sec: 500 pg/mL; 400 Sec: 100 pg/mL; 450 Sec: 50 pg/mL; 500 Sec: 10 pg/mL.

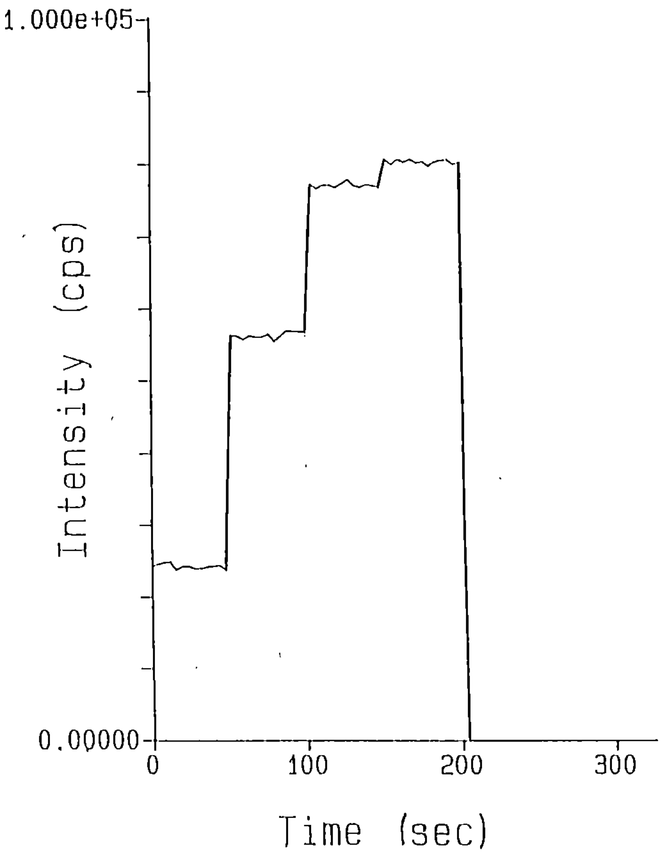

FIG. 5. Effect of anti-TNF-α antibodies on shock plasma. Monoclonal antibodies against TNFα was diluted in Na/K buffer such that 50 μL of the dilution would contain a 100-fold molar excess of antibody over TNF-α, assuming a plasma TNFα concentration of 50 ng/mL. Plasma was incubated with either antibody or an equivalent volume of buffer before incubation with H9C2 skeletal muscle cells. 0 Sec: buffer; 50 Sec: control plasma; 100 Sec: shock plasma; 150 Sec: shock plasma + anti-TNF-α antibody.

We desired an *in vitro* assay that would be sensitive to the presence of the presumptive depolarizing shock factor yet would not be subject to the same set of artifacts. Cer-

TABLE 4. *Effect of Endothelin*

	Incubation with Control Plasma	
A. Incubation	Intensity, Rat RBC	Intensity, HISM
Na/K buffer	41,000	61,400
Control plasma	120,000	87,100
Shock (1 hr)	132,900	100,000
CP + Endo 1	104,300	90,000
CP + Endo 2	102,900	88,600
CP + Endo 3	102,900	105,700

	A-10 Smooth Muscle		
B. Endothelin	Intensity(a)	Intensity(b)	Intensity(c)
Buffer	103,100	75,000	72,900
Endo 1	126,500	87,100	85,700
Endo 2	126,500	85,700	88,600
Endo 3	103,800	66,400	75,000

A: 0.1 μmol/L Endothelin (Endo) 1, 2 and 3. Control plasma (CP). B: Endothelin concentrations: (a), 1.0 μmol/L; (b): 0.1 μmol/L; (c): 0.01 μmol/L.

tain voltage-sensitive membrane dyes alter their absorbance or fluorescence linearly with changes in resting potential.[14,24,25] Fluorescence measurement of steady-state membrane potentials has been shown to be a sensitive and reproducible technique[14,26] that is not subject to the same artifacts that might limit the use of impaling microelectrodes. We chose to base our assays on the use of negatively charged oxonol dyes that tend to be excluded from the cell interior, which is itself negatively charged, rather than on positively charged dyes that tend to accumulate in the cells. Dyes that accumulate in the cell have greater toxic potential. In addition the more negatively charged subcellular membranous compartments tend to accumulate positive dyes differentially, complicating experimental interpretation.[23] To elucidate the biochemical mechanisms responsible for these physiologic phenomena, we developed an *in vitro* assay using cell-free plasma derived from hemorrhaged rats. We also required an assay with a high system throughout necessary for the many samples generated by biochemical kinetic and chromatographic procedures. However an *in vitro* assay would be useful only if there is a circulating factor that induces depolarization.

The lack of anatomic compartmentation and the metabolic simplicity of mammalian RBCs led many to question their usefulness as an experimental model of the physiology of more complex cells. However most of our knowledge of transmembrane electrolyte transport and consequent electric potential has been derived from work with RBCs.[27,28] In addition many benefits derive from the availability of RBCs in large numbers. Shires and collaborators[20] demonstrated a defect in sodium metabolism in RBCs in sepsis and in trauma patients[29] and in *in vivo* animal models.[8,19,30] This suggests that a common mechanism may underlie this phenomenon. In this report we show that *in vitro* fluorescence measurements may permit elucidation of the biochemical mechanisms mediating this defect.

We found that plasma obtained from rats after hemorrhage induced depolarization in various cell types relative to plasma obtained from rats not subject to hemorrhage. As noted above, similar depolarization was found in kidney cells regardless of whether they had undergone hemorrhagic shock. Thus conditioning of the cells during hemorrhage is not required.

To eliminate the possibility that the increased fluorescence resulted from the binding of dye to plasma proteins, we washed the cells after incubation with plasma. Nonspecific binding of dye to plasma proteins would result in an increase in fluorescence. Thus the observation that kidney cells incubated with control plasma and subsequently washed free of plasma had a lower intensity than similar cells incubated with buffer suggests that nonspecific protein binding does not account for these observations. Also because the medium was buffered to pH 7.4, changes in hydrogen ion concentration also cannot account for our observations. Except in the initial experiments, all data were obtained using naive cells, that is cells not taken from a hemorrhaged animal. The difference in response to shock *versus* control plasma of the many cell types tested implies the existence of a soluble factor(s) that is expressed differentially in the plasma of a hemorrhaged animal.

It is generally believed that in shock cellular hypoxia, usually resulting from ischemia, leads to depolarization of the cell membrane,[1] perhaps mediated by decreased production of adenosine triphosphate.[31,32] However the RBC depolarizes despite the fact that it does not depend on oxygen for metabolism. Furthermore the cells in the present study were not subjected to an experimental period of ischemia or hypoxia, so a limitation in oxygen availability to the target cell is not required for the development of depolarization. However ischemia may be required for the production of the circulating factor(s).

We sought additional evidence that the increase in fluorescence did not result from nonspecific effects of plasma proteins or ions. Figure 2 shows that the amplitude of the response initially increases with increasing dose of plasma and then saturates. Saturation is indicative of specific equilibrium receptor-binding processes. For these experiments, the normal 30-minute incubation was shortened to 15 minutes, following which the RBCs were washed free of plasma. Thus it would seem that RBCs react rapidly to plasma. For some experiments, the plasma was dialyzed overnight at 4°C *versus* Na/K buffer. Dialyzed shock plasma depolarized tested cells relative to similarly treated control plasma. These results suggest that the effective principle(s) is not an ion or other low-molecular–weight (MW) substance; rather the 10,000 MW cut-off of the dialysis membrane suggests the factor is intrinsically of high MW, or an oligomer, or exists bound as a high MW complex. In preliminary experiments we did not take special precautions against proteolytic digestion. Under these conditions a given preparation of dialyzed plasma lost ability to depolarize unpredictably with time. The addition of 1 mmol/L ethylenediaminetetraacetic acid and aprotinin (200 KIU/mL) afforded more stable preparations. These results suggest that the factor(s) either is itself a protein or is bound to a carrier protein.

Tables 1 and 2 show that a wide range of mammalian species and cell types respond to rat shock plasma. In fact every cell type tested responded positively to shock plasma. However skeletal muscle responded only after having differentiated in culture (data not shown); this may indicate maturation-dependent acquisition of the appropriate receptor. Figure 1 suggest that the circulating factor(s) exists as a readily releasable pool with indications of possible further synthesis at later time.

Both *in vitro* application of TNFα[15] and *in vivo* application of PAF[16] induce membrane depolarization. Our results (Figs. 3 and 4) indicate that these effects do not result from the direct action of these agents on the target cells. Neither TNFα nor PAF alone or in combination, even at supraphysiologic concentrations, depolarized any of the cell types tested. Furthermore monoclonal antibodies to TNFα did not affect the depolarization induced by shock plasma (Fig. 5). Heparin also was ineffective in our hands. Because the excised muscle used by Tracy et al.[15] contained blood vessels, it is possible that TNFα acted by release of a substance such as the endothelins. Endothelins gave mixed results in the depolarization assay (Table 4). None of the endothelins tested was active against RBCs. However both endothelins 1 and 2, but not endothelin 3, depolarized aortic smooth muscle, whereas endothelin 3 depolarized HISM. Because endothelin did not depolarize all the cell types affected by shock plasma, we do not think it is the sole active principle in hemorrhagic shock. Therefore we did not pursue this observation in greater detail in this study. However, if striated muscle reacts as does smooth muscle, one or more endothelins might be the final principle active in the report of Tracey et al.[15]

The observed membrane defect is associated with an increased intracellular sodium concentration.[22] To ascertain the requirement for exogenous sodium, we incubated RBCs and shock plasma either in a high sodium buffer or in a high potassium low sodium buffer. We observed that dog and pig RBCs were depolarized by rat shock plasma only in the presence of high sodium buffers (Table 1). This observation is consistent with the hypothesis that a defect in the export of cellular sodium combined with passive influx of extracellular sodium is responsible for the observed depolarization.[28]

Our results indicate a 20% to 30% increase in DIBAC fluorescence after incubating muscle cells with shock plasma. This would correspond to a 20- to 30-mV increase in the resting membrane potential, which correlates with the observations of Shires and associates.[1,8] This correlation supports our ability to use this assay to elucidate the biochemistry of hemorrhagic shock. We are using the techniques developed in this report to monitor chromatographic purification of the active principle.

Acknowledgments

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DISCUSSIONS

DR. BASIL PRUITT (San Antonio, Texas): Dr. Gann and his colleagues have presented data suggesting that a circulating toxin capable of impairing cell function is induced by hemorrhagic shock. These data supporting the earlier findings of Dr. Shires and others suggest that a humoral factor that is neither TNF nor PAF appears in the plasma within 5 minutes of shock and causes the depolarization of a wide variety of cells.

That the factor remains uncharacterized raises the possibility that it is the Phoenix of myocardial depressant factor and burn toxin, the effects of which have been attributed to salt concentration and endotoxin, respectively.

In these studies the possibility also exists, unless precautions were taken to exclude endotoxin, that this factor actually may be endotoxin absorbed from the gut or released from the liver. The dialysis procedure described does not exclude endotoxin because endotoxins are a family of substances that vary in molecular size from 10,000 to near 2.4 million daltons because of the tendency of lipid A to form aggregates.

Even though the technology used in these studies does not necessitate impalement and, therefore, injury to the cells, there are variables that influence the fluorescent intensity of oxonol dyes. The voltage-sensitive fluorescent dyes such as oxonol bind to proteins.

Because that is true, the fluorescence of the test system would increase if the protein content of the shock plasma were greater than that of the control plasma.

Similarly fluorescence is influenced by cell size and decreases as the membrane surface area per unit cell volume is increased. If exposure to shock plasma causes the volume of the cells in the test system to decrease, measured fluorescent intensity would increase, independent of other factors.

In addition the authors note that the measurement of decreased potential difference was dependent on the sodium content of the test system. Other investigators using oxonol 6 to measure membrane potentials found that as sodium concentration decreases, the transport mode of the sodium potassium ATPase pump mechanism changes from electrogenic to electroneural. And I ask whether the sodium concentration in either the plasma or in the cells in the test system varied between the control and the shock samples.

Recent studies of inside-out vesicles from red blood cells have shown that membrane potentials decrease as pH is increased. I would ask the author whether the pH of the shock plasma systematically differed from that of the control plasma.

I compliment the authors on their application of new noninvasive technology to the pathophysiology of shock. They note that preliminary studies are consistent with the factor being a protein or bound to a protein. And that raises the possibility that an antibody can be developed that will counteract the effects of the factor and reverse the cellular impairment characteristic of early shock.

DR. JAMES CARRICO (Dallas, Texas): After Dr. Pruitt's eloquent and detailed discussion, my job is fairly simple. I would like to emphasize the potential importance of this study, raise a note of caution, and then ask Dr. Gann two questions.

We have been told that there is activity in serum taken from animals subjected to shock that produces depolarization of a number of cells *in vitro.*

The importance of this study is multiple, but among the potential importance is that it validates the observations of Dr. Shires and his coworkers by totally different methodology.

It explains a number of observations that have been hanging, waiting explanation, including the difficulty of tourniquet-induced ischemia to produce similar depolarization and including some cross-circulation observations published by Trunkey when he was working in Dr. Shires' lab.

As Dr. Pruitt mentioned, it opens new avenues for understanding the pathophysiology of shock and potentially new therapeutic modalities. So the potential importance is there.

The caution is also raised by Dr. Pruitt, and that can be phrased as: Have we been here before? The myocardial depressant factor in various names and various reports has, again and again, raised our enthusiasm only to be discovered to be related to some methodologic quirk.

So the obvious question and the obvious caution is to carefully look at the methodology and determine if there some is methodologic quirk that is producing these findings.

What Dr. Gann has really showed us is that there is activity in shock serum that increases the fluorescence of cells treated with a super vital dye that is, among other things, responsive to changes in membrane potential.

Dr. Pruitt mentioned a number of other factors that can change the fluorescence of such dyes, and those need to be investigated.

My questions are very general and fairly simple. Can you give us any more infirmation about what you have done to rule out some of the other causes of alteration in fluorescence: changes in iron concentration, changes in protein concentration, changes in cell volume, changes in amount of dye attached to the cell, and changes in the nature of the fatty acids of the cell membrane itself?

Have you validated this observation by other methods; for instance administration of this serum to other animals and observation of not fluorescence of red cell membranes but rather intracellular sodium content of red cells, which would suggest this same change?

DR. DONALD S. GANN (Closing discussion): I think before I address the specific questions, I would just pick up on something that Dr. Carrico said. Namely this represents a totally independent approach to the findings of Dr. Shires and his colleagues. The fact that we ended up with the same change in transmembrane potential, the same proportional change in all the cells that we tested as has been shown by him and his colleagues over the years at least provides for me a feeling of some reassurance that we may be addressing a real phenomenon.

I tried to point out in my talk that the presence of sodium is required if the cell is to depolarize according to Dr. Shires' theory. As Dr. Pruitt noted, the NAK ATPase is electrogenic only in the presence of high sodium on the outside. That is consistent with our findings. The sodium concentration was the same in the buffer in all the experiments that I showed you, except the first one, for which we showed the requirement.

With regard to endotoxin, our current understanding of the action of the endotoxins is that they bind to a specific endotoxin-binding protein in plasma and then attach to a specific receptor on the macrophage. At the present time, this receptor has not been identified in other cells. That does not mean that endotoxin can not work on other cells, but it makes endotoxin an improbable single factor in these experiments, although we have no experiments to rule it out.

With respect to some of the vagaries of the oxonol dyes, we have attempted to deal with some of these. The cells were exposed to oxonol in their initial incubation with plasma from control or shock species and then were resuspended in a variety of solutions. In those solutions there was always the presence of dye in excess, so that the oxonol concentration available to the cells should not have been limiting.

The osmolality of the medium was held constant. So except for changes in the electrogenic pump, there should have been no control mechanism for cell volume. And that is precisely what we are trying to deal with, so it is very hard to exclude that further.

The cells were washed to eliminate extracellular protein. As Dr. Pruitt noted, if the protein were a factor in the fluorescence observed from the oxonol, we should have seen diminished fluorescence. In fact we saw enhanced fluorescence, excluding that.

The buffer solution was controlled carefully to pH 7.4 in all experiments. I doubt that pH can be a factor.

We have not done the toxicity studies that Dr. Carrico suggested. We have, instead, tried to address our current activity to isolation of this factor or factors. At the present time we have narrowed the field somewhat. Proteinase inhibitors can prevent destruction of the cell at room temperature, and we believe we have a protein—preliminary experiments with chromatography suggest a molecular weight of between 50,000 and 150,000.

We are doing a series of studies with chromatography and electrophoresis. We have about 10 candidate proteins, not all of which have activity. I can not tell you any more about what we are dealing with now. I hope it's not an artifact, but I recognize that we may be dealing with just that.

Distribution and Survival of *Escherichia coli* Translocating from the Intestine After Thermal Injury

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The present investigation was performed to study the kinetics of tissue distribution and deposition of *Escherichia coli* and endotoxin translocating from the intestine after thermal injury. *Escherichia coli* was grown in the presence of ^{14}C glucose and both labeled bacteria and endotoxin prepared from the labeled bacteria were used as translocation probes. *Escherichia coli* (10^8 to 10^{10} bacteria) and *E. coli* endotoxin (100 μg per animal) were gavaged into the stomach immediately before a 30% burn injury was inflicted in mice. Animals were killed 1, 4, and 24 hours after burn injury. Translocation occurred extensively within 1 hour after burn injury. Expressed as amount of radioactivity per gram of tissue, translocation was greatest in the mesenteric lymph node (MLN) followed by spleen, lung, and liver. Translocation of endotoxin was similar to translocation of intact bacteria, with the exception that less radioactivity could be found in the peritoneal cavity and more in the liver. Both intact *E. coli* and endotoxin translocated directly through the intact bowel wall. Killing of bacteria was greatest in the MLN and spleen, approximating 95% to more than 99% of translocating bacteria. Killing efficiency was lowest in the lungs. It is concluded that estimation of translocation by viable bacterial counts in tissues grossly underestimates the extent of translocation of bacteria and ignores the extent of translocation of endotoxin. Translocation of endotoxin may have biologic significance that is independent of and in addition to translocation of intact bacteria.

From the Transplantation Division of the Department of Surgery, University of Cincinnati Medical Center, Cincinnati, Ohio

MICROBIAL TRANSLOCATION, DEFINED as the passage of both viable and nonviable microbes and microbial products, including endotoxin, across an anatomically intact intestinal barrier, has become a fashionable topic of surgical research. This process could be, at least in part, a predisposing factor for systemic infections,[1-4] postinjury hypermetabolism,[5,6] multiple-system organ failure in seriously ill patients,[7] and clinical sepsis in the absence of a defined focus of infection.[8,9] Studies in experimental animals revealed that translocation as measured by recovery of viable organisms from regional lymph nodes is increased by agents causing direct injury of mucosal cells and by indirect injury, which is almost always associated with reduced blood flow.[10-12] In addition diseases associated with ulceration of the gastrointestinal tract are associated with recovery of viable organisms from the mesenteric lymph nodes.[10,11] Several predisposing factors for translocation have been identified, including alteration of the intestinal flora, malnutrition, immune compromise, and very young age. Hemorrhagic shock and thermal injury with malnutrition served as useful models for studying translocation. However the 'translocation' reported to occur in models of hemorrhagic shock appears to be primarily through mucosal ulcerations, whereas in models of burn injury and malnutrition, there is clear evidence for direct passage of both organisms and endotoxin through morphologically intact enterocytes.[13,14]

Because most studies of microbial translocation have been quantitated by the recovery of viable organisms from the mesenteric lymph nodes and other tissues by culture techniques, the relative rates of translocation and distribution of organisms that are killed by host defense mechanisms and the rate and distribution of translocation of endotoxin are largely unknown. The present investigation was performed to study the kinetics of tissue distribution and deposition of *Escherichia coli* and *E. coli* endotoxin translocating from the intestine after thermal injury.

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Materials and Methods

Animals and Animal Care

Adult female BALB/c mice weighing 20 to 22 g (Charles River, Wilmington, MA) were used for all experiments. They were caged in groups of five and provided food (Rodent Laboratory Chow 5001, Purina Mills, Inc., St. Louis, MO) and water *ad libidum* during a quarantine period of 1 week so they could adapt to the standard laboratory environment and to detect any pre-existing diseases. The protocols were approved by the University of Cincinnati Medical Center's Institutional Animal Care Use Committee and the animals were housed in an AAALAC-approved facility. All investigations adhered to the Guide for the Care and Use of Laboratory Animals as set forth by the Committee on the Care and Use of Laboratory Animals, National Research Council, the United States Department of Health and Human Services and the National Institutes of Health.

Preparation of Bacteria and Endotoxin

Escherichia coli (53104) was inoculated into glucose-free minimal nutrient media and grown for 19 hours at 37°C. ^{14}C glucose, 500 μCi (New England Nuclear, Boston, MA) was added to the suspension and incubated overnight. The culture was centrifuged to pellet the organisms, washed, quantitated with a Klett densitometer (Klett Mfg. Co., New York, NY), and adjusted to the desired concentration. Endotoxin was prepared and extracted from similarly labeled organisms by a previously described technique.[14]

Surgical Procedures and Burn Injury

One day before burn injury, the hair of the animal torsos was removed by clipping. Food was withheld for 18 hours but water was provided ad libidum before gavage with 0.1 mL of the translocation probe (^{14}C *E. coli* or ^{14}C endotoxin) or saline solution while the animals were awake. After gavage they were anesthetized with methoxyflurane inhalation anesthetic and a 30% full-thickness burn was inflicted using the technique of Holder et al.[15] Saline (0.1 mL) was administered immediately after burn injury for fluid resuscitation and the animals were allowed to recover from anesthesia. Groups of animals were reanesthetized at 1, 4, and 24 hours after burn, bled by cardiac puncture, and killed. Animals to be killed at 24 hours were allowed free access to food and water 4 hours after burn. Saline (1.0 mL) was injected into the peritoneal cavity and the abdomen was gently massaged to create even distribution of the fluid. The animals were prepped with 70% alcohol and aseptic techniques were used to remove the peritoneal fluid, mesenteric lymph nodes (MLN), spleen, liver, and lungs. The solid tissues (MLNs, spleen, liver, lungs) were weighed individually and homogenized after the addition of 1.0 mL of sterile normal saline. One hundred microliters of the homogenate was removed and plated on brain heart infusion (BHI) agar plates (Baltimore Biological Laboratories, Baltimore, MD) for quantatative colony counts after 18 hours of incubation. The remaining portion of the homogenate was lyophilized and clarified using a nitric acid procedure.[16] This solution was diluted 1:11 in 0.75 mol/L (molar) TRIS buffer and the disintegrations per minute (dpm) of ^{14}C in 0.5 mL was determined by liquid scintillation counting (Beckman Model LS 3133 liquid scintillation counter, Beckman Instruments Inc., Fullerton, CA). Blood was processed similarly through the decolorization procedure.

The viable colony counts were enumerated by counting and expressed as bacteria per gram of tissue or milliliter of fluid by multiplying the actual counts by $10 \times \frac{1 + \text{weight}}{\text{weight}}$. The radioactivity in tissues and fluids was expressed as dpm per gram of tissue after correction for dilution. Repeated experiments determined that approximately 1 dpm represented 121 organisms as measured by a Klett densitometer. Sample checks determined that counts by Klett densitometer approximated viable counts. Where applicable the percentage of viable bacteria in tissues and fluids was derived by dividing the observed viable bacteria by the number of estimated bacteria as determined by radioactivity in the tissues.

To determine the number of organisms that remained viable during intestinal transit, the stomach, small intestine, and colon were excised after aseptic removal of the MLNs, liver, spleen, and lungs. Each segment was washed with 1.0 mL sterile saline and the fluid was subjected to liquid scintillation counting and plate quantitation of colony counts on BHI plates.

Experimental Groups

Five experiments using 15 mice each were performed. Mice in experiment 1 were gavaged with 10^8 *E. coli* organisms per mouse, mice in experiment 2 with 10^9 organisms per mouse, and mice in experiment 3 with 10^{10} organisms per mouse. In experiment 4, mice were gavaged with 0.1 mL saline containing 100 μg of ^{14}C endotoxin. Experiment 5 was a duplicate of experiment 3. Mice were killed in groups of five 1, 4, and 24 hours after burn for determination of viable colony counts and nuclide counts in MLNs, spleen, liver, lungs, peritoneal fluid, blood, and washes from intestinal segments as described above.

Preliminary Experiments

Initial groups of animals had food withheld for 0, 6, 12, 18, and 24 hours before burn injury. The translocation rate of 10^{10} gavaged ^{14}C *E. coli* was highest in animals in which food was withheld for 18 or 24 hours, but animals

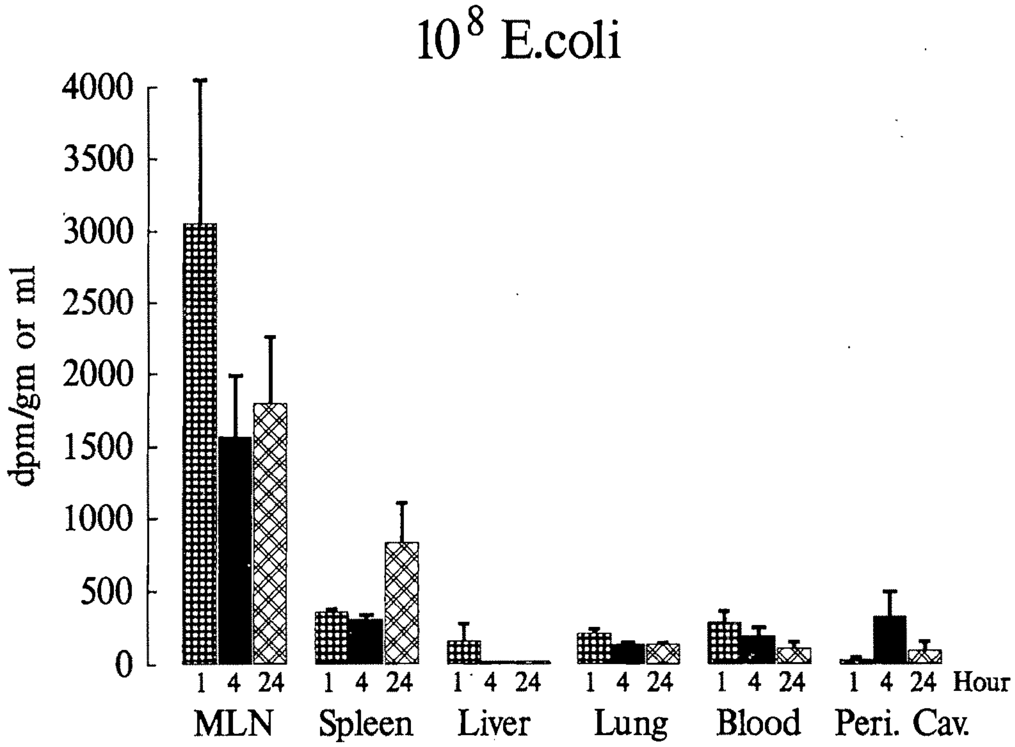

FIG. 1. Distribution of *E. coli* in tissues 1, 4, and 24 hours after gavage with 10^8 *E. coli* and burn injury as measured by dpm/g tissue or milliliters of fluid. All data in this and subsequent experiments are expressed as mean ± SEM.

deprived of food for 24 hours had a higher mortality rate. Therefore 18 hours of food deprivation was used for subsequent experiments.

Killing of animals at 1, 2, 4, and 6 hours after burn injury determined that translocation to tissues was well established by 1 hour and reached a peak no later than 4 hours. Translocation did not occur in animals gavaged with 10^{10} ^{14}C *E. coli* that were not burned.

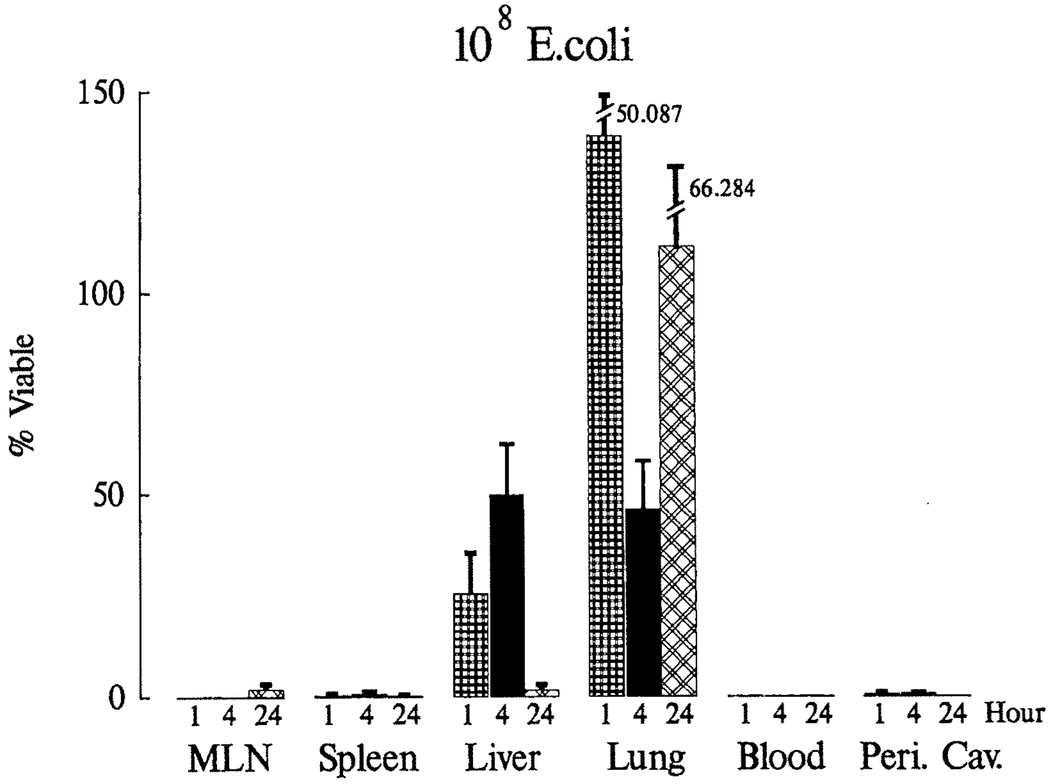

FIG. 2. The percentage of viable organisms that translocated to tissues in mice gavaged with 10^8 *E. coli* before burn.

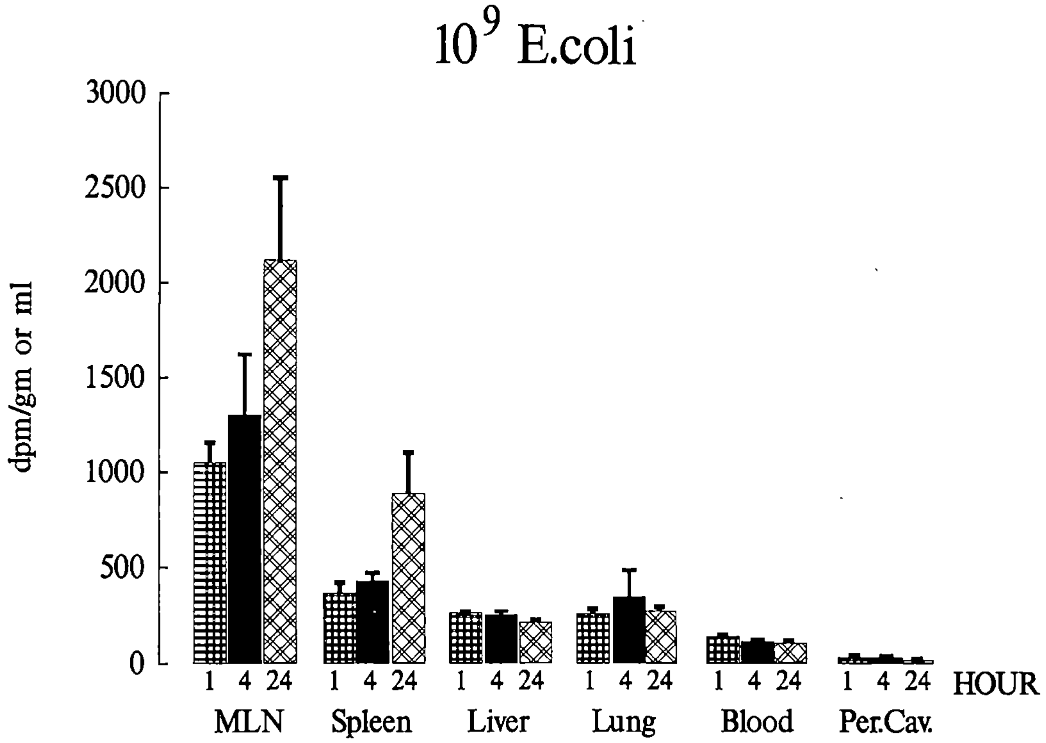

FIG. 3. Distribution of *E. coli* in tissues 1, 4, and 24 hours after gavage with 10^9 *E. coli* and burn injury as measured by dpm/g tissue or milliliters of fluid.

To determine the transit time through the intestine, animals were deprived of food for 18 hours, gavaged while awake with 0.1 mL India ink, anesthetized, burned, and killed at 1 and 4 hours after burn. By 1 hour the small intestine and cecum were filled with the India ink but none appeared in the feces. By 4 hours both feces and urine were darkly stained, as was the ileum, cecum, and colon. There was residual staining in the stomach. None of the animals had India ink grossly apparent in their lungs.

Experiment 1

The distribution of translocation as measured by radioactivity expressed as dpm per gram of tissue or milliliter of fluid is shown in Figure 1. The most concentrated activity was found in the MLNs, followed by the spleen and blood. When the percentage of organisms that remained viable was calculated for each tissue, more than 95% of those in the MLNs, spleen, blood, and peritoneal cavity were killed at each time interval. In contrast a greater percentage of organisms remained viable in the liver and, especially, the lungs (Fig. 2).

Experiment 2

Gavage with 10^9 *E. coli* resulted in a modest increase in the organisms recovered from all tissues, as shown by dpm per gram of tissue (Fig. 3). The same pattern of distribution was seen with the greatest numbers of counts found in the MLNs and spleen. When the percentage of viable organisms was calculated, similar trends were seen, generally with less than 5% of organisms surviving in the MLNs, spleen, and blood compared to higher viability in the lungs and peritoneal cavity (Fig. 4).

Experiment 3

When 10^{10} *E. coli* were gavaged, increased radioactivity was found in all of the tissues, but this was not proportionate to the increase in dose as compared to experiments 1 and 2. The pattern of distribution was similar to the previous experiments, with greater amounts translocating to the MLNs and spleen than to the liver or lung, which, in turn, were greater than the blood and peritoneal cavity (Fig. 5). Similar to experiment 2, the viability of organisms was greatest in the lungs and peritoneal cavity, with a greater percentage being killed in liver, spleen, MLNs, and blood, respectively (Fig. 6).

Experiment 4

In this experiment, animals were gavaged with 100 μg of ^{14}C endotoxin with a specific activity of 25,426 dpm per microgram. Judging from the tissue counts, shown in Figure 7, less than 0.1% of the administered radioactivity was found in the tissues at any given time, with the highest concentrations found in the MLNs, liver and lung, a somewhat different pattern from that seen for intact *E. coli.* The highest tissue endotoxin concentration, *i.e.*, in the MLNs represents approximately 0.04 μg/g tissue.

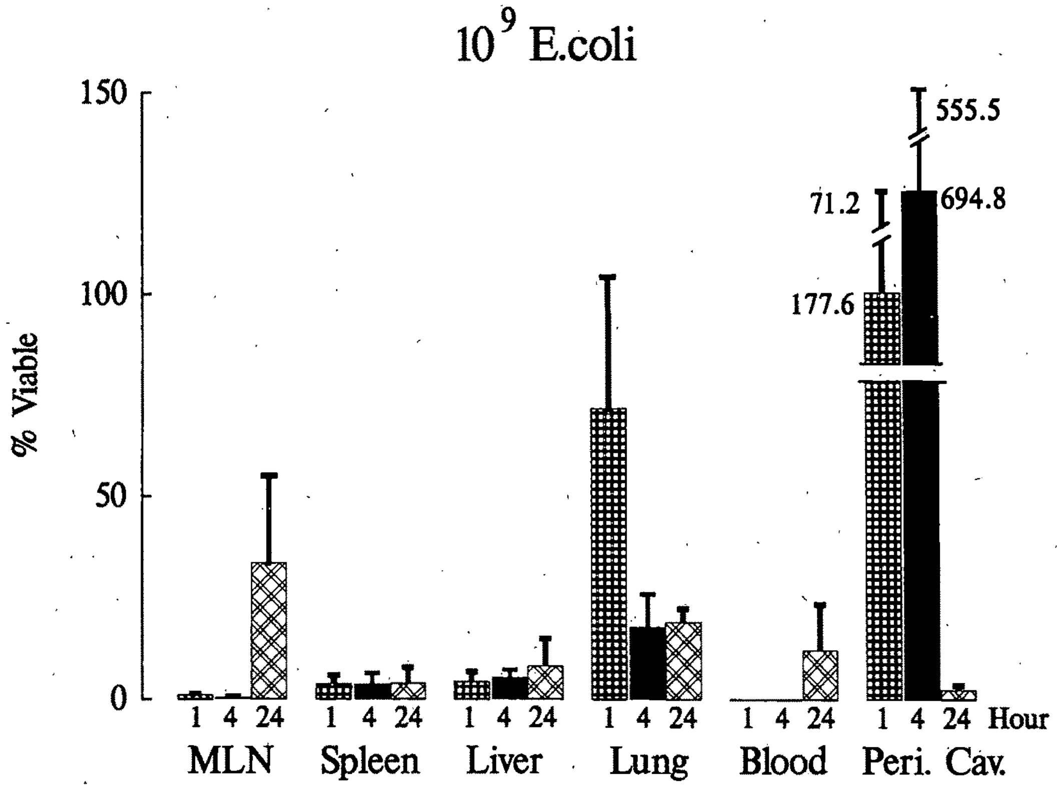

FIG. 4. The percentage of viable organisms that translocated to tissues in mice gavaged with 10^9 *E. coli* before burn.

Experiment 5

This experiment was a duplicate of experiment 3 and the data, presented in Table 1 in tabular rather than graphic form, generally confirm the findings of experiment 3, although the radionuclide counts were somewhat higher in MLNs and spleen, with a greater percentage of bacteria killed in these tissues.

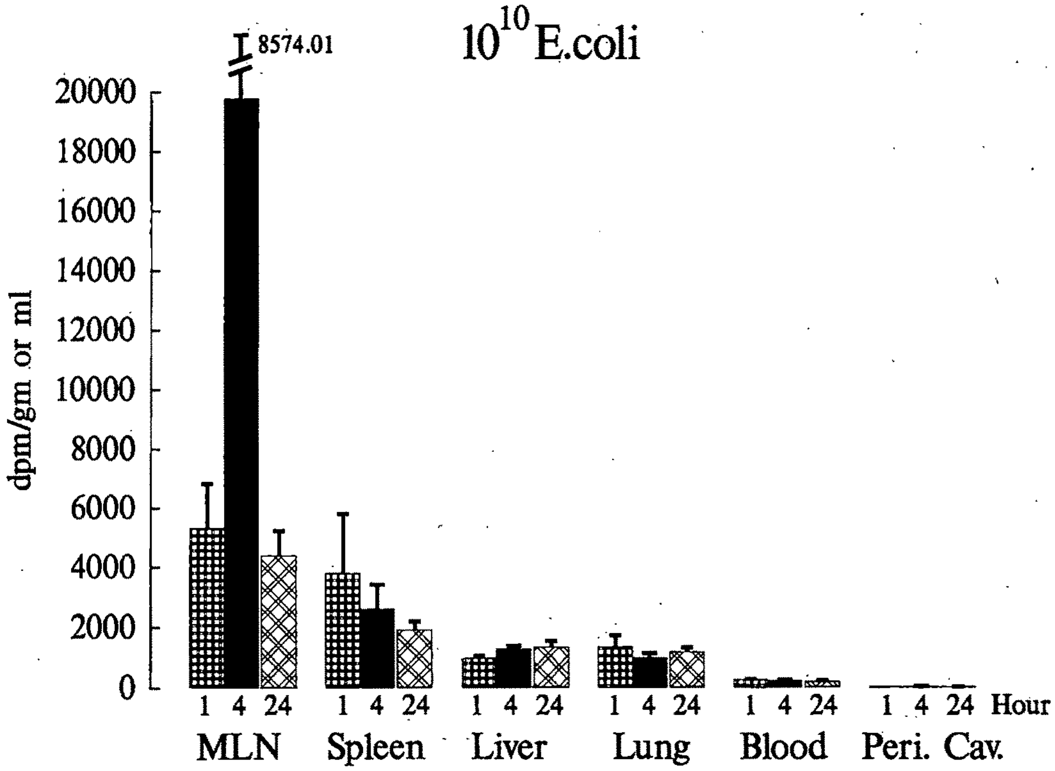

FIG. 5. Distribution of *E. coli* in tissues 1, 4, and 24 hours after gavage with 10^{10} *E. coli* and burn injury as measured by dpm/g tissue or milliliters of fluid.

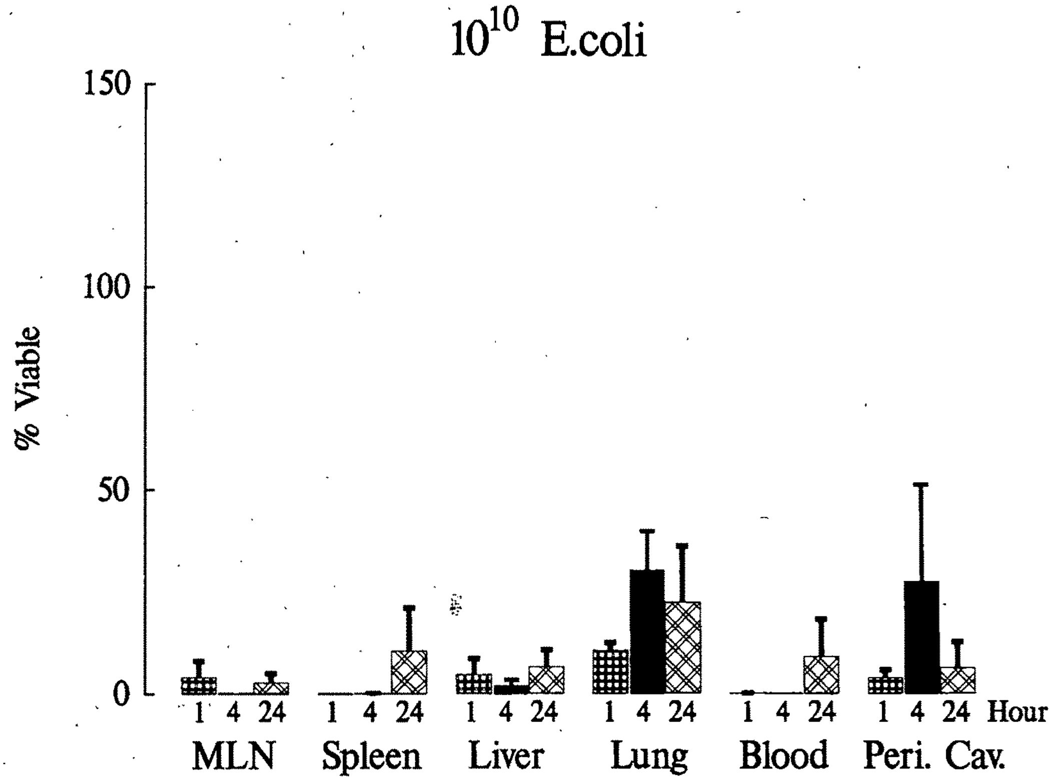

FIG. 6. The percentage of viable organisms that translocated to tissues in mice gavaged with 10^{10} *E. coli* before burn.

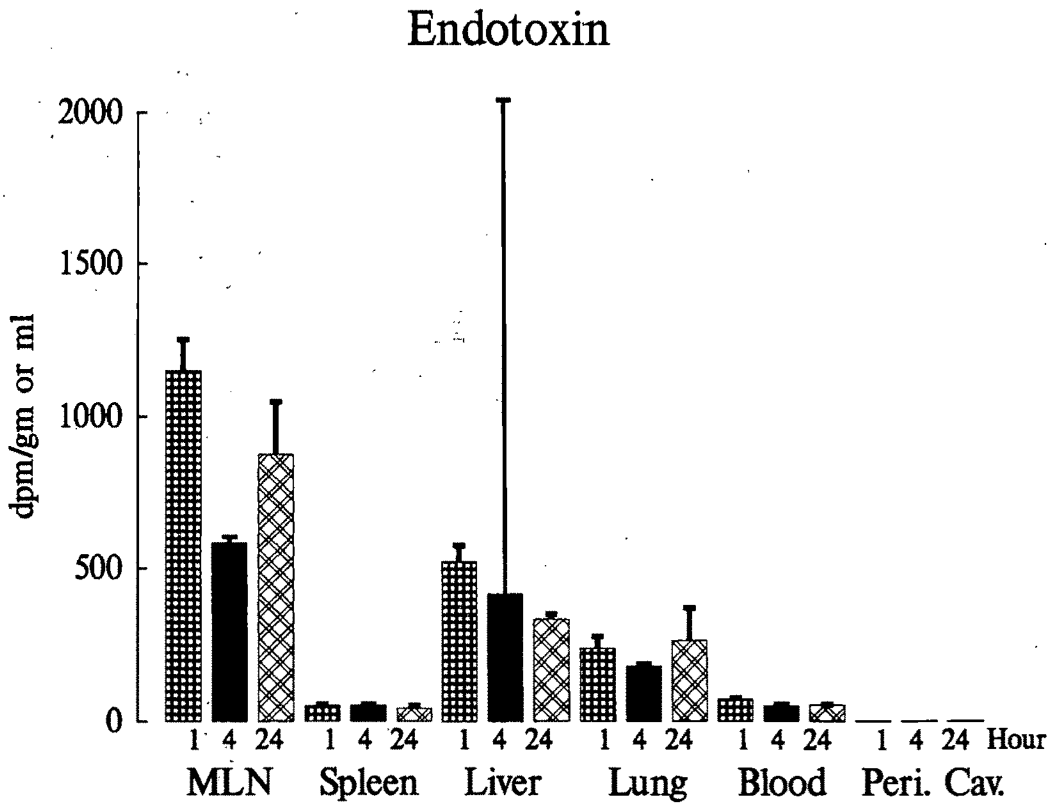

FIG. 7. Distribution of endotoxin in tissues 1, 4, and 24 hours after gavage with 100 μg ^{14}C endotoxin and burn injury as measured by radionuclide activity.

TABLE 1. *Distribution of Nuclide and Viable Bacteria for Animals in Experiment 5*

		dpm × 10^2/g or mL	Estimated Bacteria × 10^3/g or mL	Bacteria Cultured/g or mL	Percentage of Viable Bacteria
MLN	1	1519 ± 469	23,997 ± 6,145	400 ± 242	0.007 ± 0.001
	4	791 ± 157	9,571 ± 1,906	1548 ± 1116	0.01 ± 0.007
	24	279 ± 64	3,383 ± 780	787 ± 681	0.29 ± 0.26
Spleen	1	117 ± 14	1,136 ± 260	817 ± 665	0.19 ± 0.21
	4	105 ± 10	1,275 ± 106	827 ± 579	0.07 ± 0.04
	24	93 ± 7	1,132 ± 87	498 ± 431	0.04 ± 0.04
Liver	1	18 ± 3	218 ± 28	4404 ± 3645	2.08 ± 1.67
	4	17 ± 3	214 ± 40	7468 ± 3353	3.63 ± 1.46
	24	11 ± 2	134 ± 21	10,167 ± 6674	3.80 ± 2.18
Lungs	1	48 ± 12	591 ± 146	37,918 ± 8998	5.56 ± 1.26
	4	58 ± 19	708 ± 234	15,254 ± 6710	11.63 ± 3.74
	24	41 ± 9	378 ± 144	68,628 ± 35,145	20.08 ± 12.14
Blood	1	5 ± 1	59 ± 16	0	0
	4	5 ± 1	56 ± 11	0	0
	24	5 ± 0.1	62 ± 1	0	0
P wash	1	3 ± 0.7	34 ± 7	870 ± 517	4.96 ± 3.61
	4	2 ± 0.6	29 ± 8	1294 ± 989	4.73 ± 2.21
	24	3 ± 0.1	38 ± 1	1317 ± 1297	3.20 ± 3.15

Values are given as mean ± SEM.

Determination of Bacterial Viability in the Intestinal Tract

The washes of the contents of the stomach, small intestine, and colon are shown in Figure 8 as a percentage of viable bacteria related to radionuclide counts. Percentages greater than 100% found in the small intestine and colon could reflect the presence of indigenous unlabeled intestinal bacteria or growth of labeled bacteria by 4 and 24 hours. The data suggest that about one half of the bacteria in the intestinal lumen remains viable during transit. Similar values were found for the luminal washes in animals gavaged with 10^8 or 10^9 *E. coli* (data not shown).

Discussion

Translocation of bacteria from the gastrointestinal tract is a dynamic process. Most studies on translocation have used detection of viable organisms in the MLNs as well as other tissues to determine the incidence and degree of translocation. In such analyses, the major variables that influence the results are the type and quantity of bacteria in the intestinal tract, the dynamics of transport across the mucosal barrier, and the rapidity by which organisms are killed in the tissues. Using a radionuclide probe of a specific organism, such as *E. coli*, or of endotoxin derived from *E. coli* more accurately reflects the total amount of translocation to each tissue and removes, to a large extent, the differences in the rate of killing by individual animals when translocation is determined by radioactivity at a set time. However other variables are introduced, including multiplication of organisms both in the intestinal tract and tissues and redistribution of the isotope by metabolic processes of the organism and of the phagocytic cells after ingestion. The present studies suggest that perhaps one half of the organisms were viable at the time of translocation and that both organisms and endotoxin translocate very soon (within 1 hour) after burn injury. Rapid translocation of bacteria from the gastrointestinal tract also was observed by Redan et al.,[17] who showed extensive translocation of ^{14}C-labeled *E. coli* by the end of a 5-hour period of hemorrhagic shock in rats. However their study showed more translocation to the lung than to the spleen. The observation that the amount of translocated organism does not change very much between 1 and 24 hours as measured by either tissue radioactivity or viable organisms was somewhat surprising and suggests a dynamic balance between clearance of both label and viable organisms and continued translocation through the enterocytes. It is not surprising that the translocation of endotoxin followed a pattern that was similar to the distribution of intact organisms because previous studies suggested that the patterns of movement of *E. coli* and *E. coli* endotoxin through the enterocytes, lamina propria, and muscularis were similar.[14]

In these experiments, killing of translocated organisms appeared to be greatest (approximately 99% or more) in the MLNs and least (approximately 50%) in the lungs. The translocation of endotoxin appeared to be somewhat

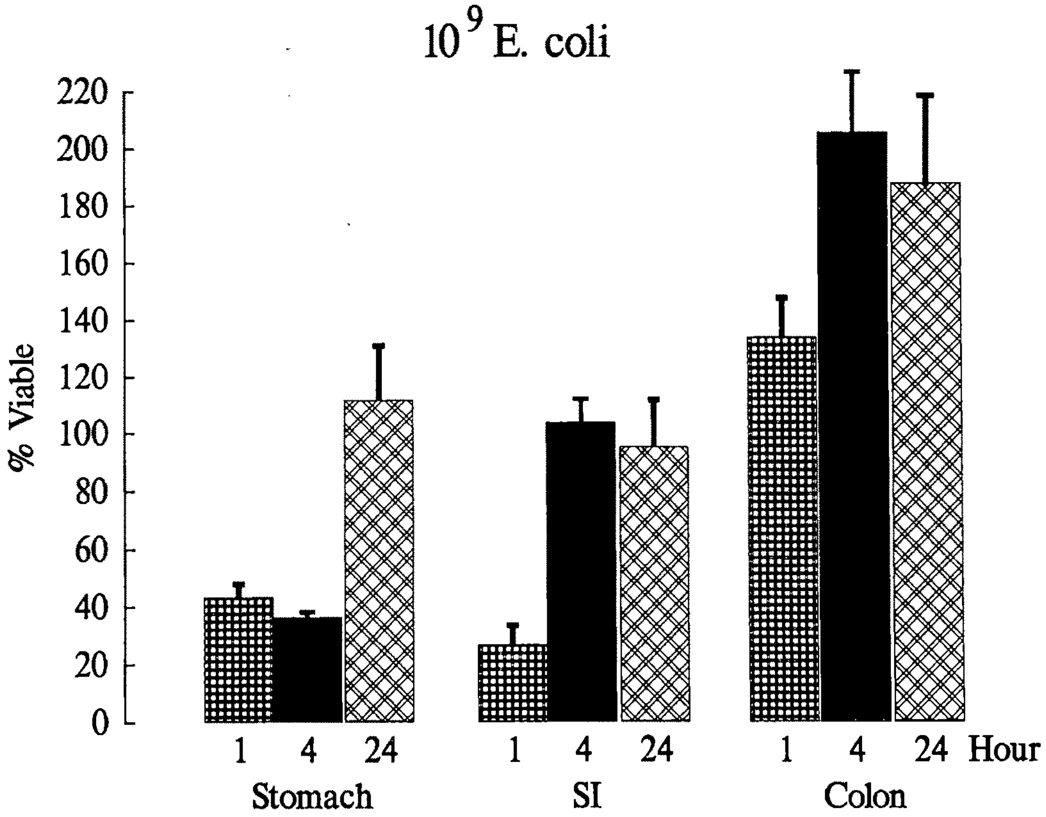

FIG. 8. The percentage of viable organisms in the stomach, small intestine, and colon as determined by actual colony counts divided by bacteria estimated from radionuclide activity is for animals gavaged with 10^9 *E. coli* before burn injury. The increase in percentage of viable bacteria after 1 hour in the stomach and small intestine could represent growth of labeled organisms, whereas the presence of indigenous organisms could account for high counts in the colon.

different from intact *E. coli* because there was more translocation to the liver and less to the peritoneal cavity. Because it is water soluble and often bound to proteins, it may be that the endotoxin that translocated to the peritoneal cavity was absorbed systemically more easily than the labeled *E. coli* trapped by peritoneal macrophages or neutrophils. Both the experiment with the endotoxin and the viable *E. coli* indicate that the biologic effects of endotoxin translocation may be much greater than could be appreciated by measurement of colony counts in the MLNs or other tissues. The concentration of endotoxin detected in tissues (up to 0.04 μg/g) is more than that necessary to stimulate macrophages and other cells *in vitro*. Because only 100 μg of endotoxin was administered and endotoxin concentrations may considerably exceed this in stool, it is very likely that endotoxin translocation is of great biologic importance independent of translocation of intact organisms. Endotoxin translocation has been shown previously by Rush et al.[18] using a hemorrhagic shock model in germ-free rats as well as others using conventional animals.[19–21] *In vitro* infection studies by Nolan et al.[22] indicated that endotoxin movement across the enterocyte was an active process involving a transport system.

These studies suggest that the use of a translocation probe, *i.e.*, the administration of a known quantity of a radionuclide-labeled bacteria or bacterial product, may be a superior way to assess differences in translocation rates across the mucosal barrier when comparing different experimental groups. An intragastric inoculum of approximately 10^{10} *E. coli* appears to be a suitable dose in this animal model. The technique has other advantages in that the relative contributions of the rate of translocation across the mucosal barrier and the rate of microbial killing by host defense mechanisms can be assessed simultaneously.

Translocation of intact organisms into the peritoneal cavity through the intact intestinal wall was shown by previous investigators, including Wells et al.[23] and Mora et al.,[24] who demonstrated that enteric organisms could be found in monocontaminated experimental intra-abdominal abscesses and intra-abdominally implanted foreign materials, respectively. Earlier studies by Papa et al.,[25] and by Booth et al.[26] suggested migration of intact bacteria through an anatomically intact intestinal wall in the presence of ischemia or obstruction. Maejima and Deitch[27] and Deitch et al.[28] also showed translocation of bacteria to the peritoneal cavity after burn injury in mice. The precise process by which organisms pass directly through the muscularis remains to be determined, although previous studies from our laboratory showed that both endotoxin and *E. coli* pass between mycocytes rather than through them.[14]

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DISCUSSIONS

DR. BEN RUSH (Newark, New Jersey): Part of my enjoyment of this paper is the chance to see some of our previous work confirmed and extended in a different model.

While there are some differences in detail between our study and Dr. Alexander's, the thrust of the two studies is much the same. Dr. Alexander has added exciting new data in quantitating the percentage of viable bacteria and the translocation of endotoxin.

As little as 3 or 4 years ago, bacterial translocation was not an accepted concept. Now it is widely accepted as a common phenomena in various types of trauma. What we now must do is quantitate its role.

My question to Dr. Alexander is, does he think this is an epiphenomena that is observed in burns but has no special effect, or is this a central part of the septic response?

DR. EDWIN DEITCH (Shreveport, Louisiana): The concept, that bacterial translocation occurs has become more accepted. Now we must focus on two questions. One is its relevance to clinical practice and the other is the mechanisms that promote and limit translocation.

As you know, we have been interested in this field for quite a while and have noticed some very fascinating observations, one of which, I think, focuses on the study that Dr. Alexander showed us today. And that is the concept that bacterial translocation is not an all or none phenomenon. We see conditions in which translocation occurs, yet the animal appears perfectly well, and in which translocation appears to be a microbiologic phenomenon. On the other hand, we see conditions in which bacteria or endotoxin ultimately can lead to gut origin sepsis, death, and a septic status.

Thus we need to understand what factors limit the systemic spread of bacteria once barrier function is lost. We believe that it is the immune system that is important. One loses barrier function, the bacteria cross; if the immune system is normal, bacterial spread is limited, but if the immune system is impaired, the bacteria may spread systematically.

Because of that I think the work that was presented today is exceptionally important in putting the ability of the host to control bacteria in perspective.

Have you done any immunologic studies to determine what it is that allows these bacteria to survive and, conversely, what it is that allows these bacteria to be killed?

The concept of the multi-insult model, I think, applies here because this was a starved animal that required both a burn injury and inoculation with bacteria to see systemic translocation. Would you comment on that?

Next, would you tell us a little bit about the *Escherichia coli*? Was this a pathogenic *E. coli* or a normal benign strain? Do you think the probe that you used for the bacteria is important? Have you done anything to reverse the process?

Last I ask you about the question of genetic susceptibility to injury. As you know, we have looked at burn injuries in different strains of mice and found that the BALB/c is uniquely susceptible to thermal injury and thermal injury-induced loss of barrier function. So I wonder if you have any thoughts about this or have looked at other strains.

Dr. David Herndon (Galveston, Texas): Dr. Alexander has again impressively added to his groundbreaking work on translocation of bacteria and endotoxin from the GI tract after burns.

This really is a landmark paper for he has, for the first time, identified for us the startling proportion of nonviable bacteria that translocate and have heretofore not been recognized because our standard essays have been for viable bacteria almost exclusively.

The significance of this finding is that massive early dead bacterial or endotoxin translocation load can prime a burn victim's defense system to respond in a more exaggerated fashion to subsequent insults.

Most impressive, also, is the fact that the highest percentage liability for bacteria in this study was in the lung, which can implicate translocation as the most significant contributor to ICU acquired pneumonias in burn patients.

I did notice that although this phenomena occurred at every dose of *Escherichia coli*, it was less at the higher dose, which is a paradox I wish Dr. Alexander would further elucidate.

These studies confirm the time course studies previously reported by Drs. Saydjari and Townsend that have shown rapid repair of GI mucosa as demonstrated by DNA, polyamine, and ODC content after acute burn injury, indicating that the phenomena of bacterial translocation occurs extremely early in the first hour or two after injury, with almost complete recovery of the gut by 12 to 24 hours after injury.

A comment about the clinical significance of this finding should be made. We have been demonstrating in animals translocation in several different animal models. But there is a large clinical study recently reported by the Moores from Denver, in which they placed catheters into the portal vein of a large group of patients who were at very high risk for multiple-organ failure and whom we would have expected would be the most clinically relevant model for translocation. Although they found a 25% incidence of positive bacterial cultures in the mesenteric lymph nodes of these patients, they found no bacteria or endotoxin in portal vein cultures.

I would ask Dr. Alexander to comment on this clinical study. Could the need for prolonged fasting, as was present in this model, explain the paradox? Perhaps two insults are required for translocation to become clinically significant.

Dr. J. Wesley Alexander (Closing discussion): There is, of course, the persistent question of the biologic relevance of translocation. I believe that must await further investigations. It is fairly obvious, however, that translocation does not play a significant role in normal, healthy individuals.

The study of Moore is of particular interest, and in that they showed, as Dr. Herndon indicated, there was little evidence of recovery of bacteria from the portal vein by a portal vein cantilation to the omphalomesenteric vein in patients with traumatic injury. This may be due to a couple of reasons. One is that that particular group is very dedicated to aggressive resuscitation of patients, preventing shock as much as possible, which Dr. Rush has, of course, shown is a very important model for producing translocation. And they also have been very aggressive in early enteral nutrition, which we and others have shown are important factors in reducing the translocation rate. Their model in humans may not have shown much evidence of translocation because of their very effective post-traumatic treatment of the patients.

It may be important to note that translocation of endotoxin may actually be a helpful phenomenon. As most of you will realize, there has been an extreme effort in the past few years to investigate biologic immune modifiers that will improve host defense after a variety of types of injury and infection. For the most part, these experiments have not been very helpful and have not led to products that will be very effective, at least at the clinical level.

Perhaps one of the reasons is that because in experimental models endotoxin itself is a very important and potent modifier that will improve resistance to infection if given in doses that are not enough to cause shock. So in fact translocation of endotoxin may be helpful in stimulating immune responses and protection against infection in the early post-traumatic period.

However prolonged exposure to endotoxin and to bacteria may occur in certain groups of patients such as those admitted to the intensive care unit with persistent underperfusion of tissues and lack of enteral nutrition may have a particular susceptibility to the adverse effects of the translocation process.

Certainly it is clear it is not important in everyone.

As far as the immulogic studies that Dr. Deitch asked about for controlling killing by the host, we have not effectively addressed those questions yet, although others have shown that steroids, as an example, given to animals may increase the rate of translocation, as indicated by recovery from the mesenteric lymph nodes. This may simply reflect a decrease in the killing at those areas.

The *E. coli* we use is pathogenic, and we deliberately use the BALB/c mice based on his studies, which show that it is an appropriate model if we wish to show translocation.

As far as reversing the process is concerned, it is clear that enteral nutrition provides protection against the translocation process, and this has been used effectively in a variety of clinical studies, including that of Drs. Moore in Denver to decrease translocation and to decrease the rate of infection in traumatized patients.

Investigations in the laboratory have shown a variety of other substances, such as glutamine, may decrease translocation in certain models. Prostaglanden analogues, particularly the E series, may do it, and certain trophic hormones such as bombesin may do it.

Propranolol Diminishes Extremity Blood Flow in Burned Patients

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Beta adrenergic blockade diminishes the catecholamine-mediated elevations in heart rate and myocardial contractility that characterize postburn hypermetabolism. To examine how these alterations in cardiac performance affect peripheral perfusion, indirect calorimetry and leg blood flow were measured before and then after a 2-hour intravenous propranolol infusion. Five severely burned patients (55% + 7% total burn surface area), given propranolol at 8 μg/kg/minute, had a significant reduction in cardiac index and heart rate with an increased leg vascular resistance resulting in a decrease in extremity perfusion. Four healthy volunteers were given propranolol at 5 μg/kg/minute, resulting in a comparable decrease in heart rate, yet there was no change in leg vascular resistance or extremity perfusion. In both patient groups, propranolol decreased the plasma lactate concentration. This suggests that in hypermetabolic patients, beta adrenergic blockade reduces peripheral perfusion and that peripheral perfusion is not a principal determinate of plasma lactate levels. Rather adrenergic blockade appears to decrease lactate concentration as a consequence of the inhibition of lipolysis.

THE TREMENDOUS OUTPOURING of catecholamines after a thermal injury appears, in part, to mediate the hyperdynamic, hypermetabolic stress response.[1] In attempting to blunt this response to catecholamines, beta adrenergic antagonist has been administered with controversial efficacy. In an extensive evaluation of the relationship between catecholamines and metabolic rate in burn patients, Wilmore et al.[1] demonstrated a significant correlation between increasing urinary catecholamine excretion and an increasing metabolic rate induced by cold stress. They also identified four severely burned patients in whom cold failed to induce the catecholamine-mediated stress response and resulted in a paradoxical decrease in the metabolic rate. All four nonresponding patients later died of burn-related complications. Consequently Wilmore et al.[1] deduced that the catecholamine-mediated elevation in metabolic rate may be appropriate and integral for recovery after a major burn. Furthermore Goodall et al.,[2-4] in a series of studies, showed that the increased turnover and excretion of catecholamines after thermal injuries can deplete the adrenal medulla of catecholamines and reduce monoamine stores in sympathetic ganglia. They concluded that supplementation of adrenergic precursors may be beneficial in maintaining catecholamine synthesis and ensuring an adequate stress response and continued hypermetabolism. In contrast Herndon et al.[5] demonstrated that limited beta adrenergic blockade in burn patients may be beneficial by reducing myocardial work. In that study propranolol failed to decrease the resting energy expenditure and the overall hospital course and mortality rate were clinically unaffected. However propranolol did significantly increase urea production and may paradoxically augment protein catabolism. The purpose of this study was to assess the impact of reduced cardiac performance by beta adrenergic blockage on peripheral perfusion and lactate metabolism in severely burned hypermetabolic patients compared to normal healthy volunteers.

Materials and Methods

Subjects

Five severely burned and four healthy young men of similar size and age participated in this study as approved by the Institutional Review Board of the University of

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TABLE 1. *Patient Characteristics (Age, Size, and Severity of Burn) for Both Patient Groups*

Characteristics	Normal Controls (n = 4)	Burn Patients (n = 5)
Age (yrs)	26 ± 2	21 ± 3
Weight (kg)	72 ± 4	72 ± 9
BSA (m^2)	1.91 ± 0.07	1.88 ± 0.13
Leg volume (L)	16.2 ± 1.2	13.0 ± 1.9
%TBSA burn	0	65 ± 7
%Full-thickness burn	0	45 ± 11
%Leg burn mean ± SEM	0	65 ± 15

BSA, body surface area; TBSA, total body surface area; SEM, standard error of the mean.

Texas Medical Branch (OSP-89-144) (Table 1). The patients were similar in extent and severity of burn and were studied approximately 2 weeks after injury. Increases in resting energy expenditure, cardiac index, and heart rate confirmed that these patients were hypermetabolic and hyperdynamic (Table 2). Standardized treatment protocols for initial fluid resuscitation, formulated nutritional support, and manner of operative care with early burn wound excision and serial autographing allowed uniformity in patient care.[5,6] The volunteers were considered healthy by screening history, physical examination, and blood analysis. All were normal for height and weight and were not receiving any medications.

Study Protocol

The study was begun in the morning following an overnight fast. In addition the burn patients had all enteral and parenteral nutrition discontinued 6 hours before initiating this study. Resting energy expenditure was assessed by indirect calorimetry using a metabolic cart (SensorMedics MMC Horizon System 4400, Anaheim, CA). Placement of femoral arterial and venous catheters allowed for pressure monitoring and serial blood sampling. Cardiac output was determined in the burn patients with a 5-mg bolus injection of indocyanine green dye *via* the central venous access and measurement of dye dilution from the femoral artery. Central venous access was not placed in the normal volunteers and precluded measurements of cardiac output. Leg blood flow also was determined by bolus dye dilution.[7] This entailed injection of a 5-mg bolus of indocyanine green dye into the femoral artery as blood was being aspirated from the femoral vein through a spectrophotometer (Fig. 1). The depreciation of the spectrophotometric measurement then reflected extremity perfusion as quantitated by a pediatric cardiac output computer and confirmed graphically (Lyons Medical Instruments Corp., Van Nuys, CA). The values for leg blood flow by this method were similar to results reported for age- and size-matched normals by the continuous-infusion dye dilution method[8] and for normals and patients with severely burned legs determined by plethysmograph.[9] Leg volume was assessed by the integration of several circumference measurements at 5-cm intervals with the length of the calf, thigh, and foot.

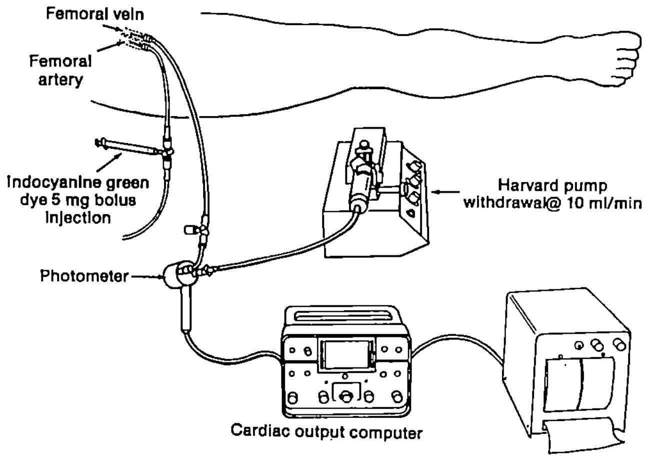
Femoral vein
Femoral artery
Indocyanine green dye 5 mg bolus injection
Harvard pump withdrawal@ 10 ml/min
Photometer
Cardiac output computer

FIG. 1. Schematic diagram of bolus dye dilution method for determining leg blood flow.

After baseline protocol measurements and blood sampling, propranolol was administered for 2 hours intravenously at 8 μg/kg/minute in the burn patients and at 5 μg/kg/minute in the healthy volunteers. These amounts

TABLE 2. *Hemodynamic Alterations for Both Patient Groups and Their Response to Propranolol*

Hemodynamics	Controls		Burn Patients	
	Basal	Propranolol	Basal	Propranolol
Heart rate (beats/min)	57 ± 2	47 ± 1†	134 ± 4*	101 ± 4†
Mean arterial pressure (mmHg)	103 ± 6	100 ± 3	91 ± 3	82 ± 2
Leg blood flows (mL/min)	3.3 ± 0.5	3.3 ± 0.6	10.9 ± 1.6*	8.5 ± 1.3†
Leg vascular resistance (torr/mL/min)	32.4 ± 4.5	31.7 ± 5.9	8.4 ± 1.1*	9.7 ± 1.1†
Cardiac index (L/min/m^2) (normal range, 2.4–4.8)			6.3 ± 0.3	5.0 ± 0.1†

Mean ± SEM.
Leg measurements standardized for 100-mL leg volume.
* $p < 0.05$ compared to basal controls (Student's independent t test).
† $p < 0.05$ compared to group basal (Student's paired t test).

had been determined previously to reduce heart rate by approximately 20% for each group by completion of the infusion. After 2 hours of propranolol infusion, measurements of cardiac output, leg blood flow, indirect calorimetry, and blood sampling were repeated. Blood samples were analyzed for concentrations of glucose and lactate (Beckman Instruments Auto Analyzer, Fullerton, CA). Plasma catecholamine levels were quantitated by radioimmunoassays at an independent laboratory (SmithKline Beecham Clinical Laboratories, Van Nuys, CA). In the burn patients, urine was collected from an indwelling Foley catheter. All voided urine was collected from the volunteers. Total urinary nitrogen was determined with an Erba nitrogen analyzer (Carlo Erba Instrumentation, Rodono, Italy).

Calculations

Extremity vascular resistance was derived from leg blood flow and pressure measurements. Blood flow was standardized for 100-mL leg volume.

LVR = 80 (MAP—MVP) LBF

Where: LVR = leg vascular resistance (dynes sec/cm^5 m^2 100 mL)

MAP, MVP = mean arterial, venous pressures (mmHg)

LBF = leg blood flow (L/minute 100 mL)

Net balance for lactate and glucose was also standardized for leg volume.

NB = LBF ([ART]—[VEN])

Where: NB = net balance (mmol/L/minute 100 mL)

LBF = leg blood flow (L/minute 100 mL)

[ART] [VEN] = arterial, venous concentrations (mmol/L)

A negative net balance then reflects net release of lactate or glucose from the limb.

Student's independent t test was used for statistical comparison between patient groups, while the Student's paired t test was used to assess variations within each group between basal and beta adrenergic blockade. Results were presented as mean ± SEM and $p < 0.05$ was accepted as significant.

Results

Volunteers were well matched for size and age with the burn patients and all the subjects studied were male (Table 1). The burn injury was both extensive (65% ± 7% mean total burn surface area) and severe (45% ± 11% full-thickness burn). There was, however, a wide range in the extent of burn involving the studied leg (range of percentage of burned leg: 10% to 98%). Multiple regression analysis failed to correlate any relationship between the percentage of leg burned to the extremity blood flow or to lactate or glucose net balance. Combined early excision of the burn wound and the use of available unburned area for donor site resulted in the vast majority of the extremity studied being an open wound. This resulted in legs with open wounds of similar size and appears to have minimized any potential differences due to variations in the percentage of leg burned.[10]

The burn patients were extremely hyperdynamic, as demonstrated by basal heart rates greater than 130 and a twice-normal elevation in cardiac index. The heightened cardiac performance combined with the reduced vascular resistance of the leg produced a significant elevation in extremity perfusion (Table 2). Propranolol (8 μg/kg/minute, 2-hour intravenous infusion) lowered the heart rate by 25% ($p < 0.05$) and significantly reduced the cardiac index (Table 2). Furthermore propranolol altered extremity perfusion with an increase in leg vascular resistance and a decrease in leg blood flow. In contrast, while the propranolol infusion (5 μg/kg/minute, 2 hours) in the normal volunteers reduced the resting heart rate by 18% ($p < 0.05$), it failed to alter leg blood flow or vascular

TABLE 3. *Alterations in Lactate and Glucose Metabolism for Both Patient Groups and Their Response to Propranolol*

Lactate/Glucose Metabolism	Controls		Burned Patients	
	Basal	Propranolol	Basal	Propranolol
Lactate (mmol/L)				
Arterial	0.80 ± 0.04	0.69 ± 0.04†	1.79 ± 0.28*	1.43 ± 0.24†
Venous	0.90 ± 0.04	0.78 ± 0.05†	2.11 ± 0.30*	1.78 ± 0.28†
Lactate net balance (mmol/min)	−0.29 ± 0.15	−0.21 ± 0.16	−3.92 ± 1.58*	−3.07 ± 0.80
Glucose (mg/dL)				
Arterial	80 ± 2	79 ± 3	104 ± 6*	97 ± 5
Venous	79 ± 1	78 ± 2	103 ± 5*	97 ± 7
Glucose net balance (mg/min)	0.2 ± 0.4	1.3 ± 0.6	0.8 ± 1.7	0.1 ± 2.2

Mean ± SEM.

Net balance measurements standardized for 100-mL leg volume.

* $p < 0.05$ compared to basal controls (Student's independent t test).

† $p < 0.05$ compared to group basal (Student's paired t test).

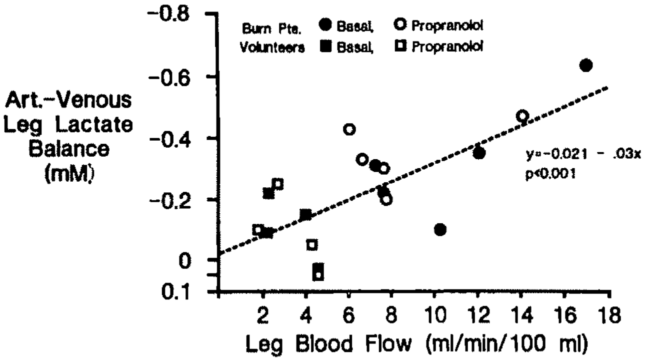

FIG. 2. Relationship of leg blood flow to lactate balance across the leg.

resistance (Table 2). The disparate dosage of propranolol between patient groups did produce similar percentage reductions in heart rate. Continuous telemetry during the propranolol infusion did not identify any cardiac arrhythmias other than sinus bradycardia in the healthy volunteers.

Both arterial and venous plasma lactate concentrations from the burn patients were elevated significantly above the lactate levels in the healthy volunteers (Table 3). Plasma samples obtained after the propranolol infusion demonstrated a significant reduction in lactate levels for both arterial and venous samples and in both groups. Also the net release of lactate from the leg was significantly greater from the burned extremities compared to the normal legs. Beta adrenergic blockade resulted in only an insignificant decrease in the negative net balance of lactate from the leg for both burned patients and controls (Table 2). Furthermore the increase in extremity blood flow correlated with an increasing arterial, venous concentration gradient for lactate across the leg ($p < 0.001$) (Fig. 2). This correlation was valid for both the burn patients and the normal controls and during basal and propranolol therapy. Common with severe burns, plasma glucose concentrations were greater in the burn patients[11]; however propranolol had no significant effect on plasma glucose concentrations or on the net balance of glucose across the leg (Table 3). This suggests that the alterations in lactate with beta adrenergic blockade are not a consequence of changes in glucose homeostasis.

The fasting burn patients were hypermetabolic when studied 2 weeks after injury, with resting energy expenditures nearly 40% greater than predicted for normals by the Harris Benedict formula ($p < 0.05$). These patients also had significantly greater urinary nitrogen loss than the controls (Table 4). Neither of these parameters in either burn patients or volunteers changed with the beta adrenergic blockade. Indirect calorimetry demonstrated higher oxygen consumption for the burn patients while the fasting respiratory quotient was similar for both the burn and control subjects. Propranolol had no effect on the oxygen consumption or the respiratory quotient (Table 4). Plasma levels of epinephrine and norepinephrine in the burn patients were more than double both the normal range and the control group ($p < 0.05$). The plasma concentration of norepinephrine was not effected by propranolol in either group. While there was an insignificant increase for the volunteers, propranolol significantly increased the epinephrine levels for the burn patients (Table 5).

Discussion

Burn injury results in increased levels of catecholamines, which then are partially responsible for the tachycardia and increased cardiac index observed after burns.[1] This experiment demonstrated that leg blood flow also was increased after burns and is due not only to an accelerated cardiac performance but also to the diminished vascular resistance from beta adrenergic vasodilatation. Beta adrenergic blockade blunted the postburn hyperdynamics with significant reductions in cardiac index with a concomitant increase in vascular resistance.

TABLE 4. *Measurements of Energy Expenditure and Urinary Nitrogen for Both Patient Groups and Their Response to Propranolol*

	Controls		Burn Patients	
Metabolic Rate	Basal	Propanolol	Basal	Propranolol
Resting energy expendiure REE/m^2	866 ± 35	932 ± 28	1289 ± 137*	1278 ± 95
% REE/predicted REE‡	0.91 ± 0.04	1.03 ± 0.02	1.39 ± 0.16*	1.38 ± 0.12
Oxygen consumption (mL/kg min)	3.32 ± 0.16	3.48 ± 0.28	4.96 ± 0.61†	5.10 ± 0.59
Respiratory quotient	0.82 ± 0.01	0.81 ± 0.01	0.80 ± 0.01	0.79 ± 0.02
Urinary nitrogen (g/d)	9.5 ± 2.6	9.9 ± 32	33.1 ± 1.0*	27.6 ± 1.7
No. days study after burn			15 ± 1.2	

Mean ± SEM
* $p < 0.05$ compared to basal controls.
† $p = 0.05$.
‡ Predicted REE calculated from Harris–Benedict equation.
REE, resting energy expenditure.

TABLE 5. *Catecholamine Levels for Both Patient Groups and Their Response to Propranolol*

	Controls		Burn Patients	
Catecholamine Levels	Basal	Propranolol	Basal	Propranolol
Norepinephrine (pg/mL) (normal range, 110–410)	302 ± 21	280 ± 54	1009 ± 145*	814 ± 152
Epinephrine (pg/mL) (normal range < 50)	61 ± 31	76 ± 16	133 ± 17*	207 ± 4†

Mean ± SEM.
* $p < 0.05$ compared to basal controls.
† $p < 0.05$ compared to group basal.

These alterations in hemodynamics resulted in a diminished leg blood flow, yet despite this reduction in extremity perfusion, urinary nitrogen excretion and the net balance of lactate from the leg were not affected by the beta adrenergic blockade.

By reducing extremity perfusion, beta blockade eventually may increase catabolism. While urinary nitrogen excretion was not acutely affected in this study, a prolonged reduction in peripheral perfusion with repeated administration of propranolol may explain the increase in urea production seen with chronic beta blockade reported by Herndon et al.[5] We suggest that propranolol reduces peripheral perfusion during stress physiology by a combination of reducing cardiac index and by increasing vascular resistance. This corroborates a Scandinavian study in which intra-arterial infusion of adrenaline into the femoral artery of healthy volunteers doubled extremity blood flow *via* a decrease in leg vascular resistance.[8] Beta blockade before the adrenaline infusion obviated any change in leg vascular resistance or blood flow. These studies suggest that the elevation in catecholamines observed after injury mediates peripheral vasodilatation, which augments extremity perfusion. This selective increase in epinephrine levels with beta adrenergic blockade previously was reported for healthy controls by an undetermined mechanism.[12] In contrast Aulick et al.[10] demonstrated with venous plethysmography that blood flow in the unburned leg of otherwise severely burned patients was similar to normal controls. Assuming that the systemic catecholamines were effecting equally the vascular resistance of both the burned and unburned extremities, then the presence of the wound appears to be essential for the catecholamine-mediated decrease in leg vascular resistance. Because the patients in this study had open leg wounds of similar magnitude, the importance of the wound in determining leg blood flow and the sensitivity of the vasculature to catecholamines cannot be addressed.

This experiment also addresses the effects of the postburn hyperdynamic hypermetabolism on lactate kinetics. If it is assumed that increases in lactate production are related to the acceleration of anaerobic glycolysis after thermal injury, then a decrease in peripheral perfusion will increase lactate production. Because this study demonstrated the opposite, *i.e.*, that increased extremity blood flow is related to an increased net release of lactate from the leg, the supposition that lactate production is related inversely to the availability of oxygen for continued aerobic glycolysis appears unlikely. Also, while beta blockade significantly reduced cardiac index and plasma lactate in this study, whole-body oxygen consumption remained unchanged. This correlates with the findings of Wilmore et al.,[9] who observed that leg blood flow and lactate production correlated with the extent of the leg wound but was not associated with any changes in limb oxygen consumption. It is plausible, though, that a stimulated rate of glycolysis results in excess pyruvate production (as shown by Wolfe, et al.[13]) in quantities greater than can be consumed by the pyruvate dehydrogenase (PDH) enzyme complex. As a consequence excess pyruvate is shunted to lactate resulting in higher plasma lactate concentrations. Elevations in the rate of glycolysis after burns have been well documented with the result that pyruvate production is accelerated.[14,15] Furthermore recent animal studies have identified alterations in the PDH enzyme complex during bacteremia resulting in a decrease in pyruvate oxidation.[16,17] If the efficiency of this enzyme complex also is decreased after burns, additional shunting of pyruvate to lactate would occur.

In this study beta blockade significantly lowered the plasma lactate concentrations both in healthy men and in postburn patients. Wolfe et al.[15] demonstrated that the glycolytic-gluconeogenic cycling was not altered by propranolol in burn patients and implied that beta blockade does not lower lactate levels by decreasing the production of pyruvate. However that same study did show that the accelerated rate of lipolysis after thermal injury was reduced significantly by propranolol. Kaiser et al.[18] suggested that accelerated fat oxidation results in increased production of acetyl CoA and citrate. Accumulation of acetyl CoA then may retard pyruvate oxidation by inhibiting PDH. Propranolol thus appears to decrease the percentage of acetyl CoA formed by fat oxidation and results in increased pyruvate oxidation. Therefore beta blockade may diminish lactate production by inhibiting lipolysis.

This experiment, however, did not identify a significant increase in the respiratory quotient with propranolol administration coincident with the decrease in lactate. This lack of effect on respiratory quotient, despite the inhibition of lipolysis, can be explained by noting that the increased triglyceride, fatty acid cycling in burn patients results in a great excess of lipolysis relative to the concentration of fatty acids required for oxidation. Even in healthy volunteers, 70% of the free fatty acids generated by lipolysis are re-esterified.[19] As a consequence lipolysis can be significantly reduced without greatly affecting the respiratory quotient and reiterates that glucose availability, and not the availability of fatty acid, is the predominant determinant of the respiratory quotient.

The clinical significance of this study demonstrates that propranolol can blunt the cardiac and peripheral vascular response associated with postburn hypermetabolism. These reductions in cardiac performance and peripheral perfusion correlated with reduced lactate production and lower blood lactate concentrations. If these effects can be sustained without adverse consequences on energy expenditure or protein metabolism, beta adrenergic blockade may indeed warrant a clinical application in treating severely burned patients.

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DISCUSSIONS

DR. GIL WARD (Miami, Florida): I rise to ask the heretical philosophical question: Why do you want to change the metabolic response? Are you sure an increased cardiac output, a decreased peripheral resistance, and an increased lactate production are bad?

The metabolic rate is unquestionably elevated, and to date we only know its consequence, not its absolute cause. I have always been uncomfortable attempting to blunt a physiologic response until I am certain the response is detrimental to the patient. And herein lies the conundrum. What is normal for an abnormal circumstance?

I am not suggesting we should avoid putting out physiologic fires. But in similar sense, we should not avoid allowing a physiologic break fire.

I have three questions, the first regarding technique and model. Why do the authors think an excised burn wound or an open donor site are equivalent to nonexcised burn wounds?

My experience is that patients with clean, open, excised wounds and donor sites are better and on the road to recovery, acting well when compared to patients with wounds partially unexcised at a 2-week postinjury period.

Second at 2 weeks after injury, a 65% total body surface area burn is well into a period of septic complications and influences. What was the condition of these burn patients regarding sepsis at the time of study?

And, third, if the amount of lactate production is truly dependent on the burn wound size, in artificially reducing its production by pharmacologic manipulation, might you be shutting off the only metabolic means by which the injured tissue can survive?

DR. BASIL PRUITT (San Antonio, Texas): I would like to compliment Dr. Gore and his colleagues on this study, which extends their earlier observations on the hemodynamic and metabolic response of burn patients to beta adrenergic blockade.

Although the authors found that propanolol infusion exerted no statistically significant effect on net glucose balance in the limbs studied, it should be noted that in their table net balance decreased by a factor of eight, that is, from 0.8 to 0.1. I wonder whether the lack of statistical significance is a type two error due to the small number of patients studied.

The lack of effect of propanolol and the net balance of glucose across the leg is somewhat puzzling because one might anticipate that propanolol would counteract epinephrine inhibition of insulin secretion and increase glucose uptake.

The fact that epinephrine increased significantly in the propanolol-treated patients may have prevented that anticipated effect of propanolol.

And it would be interesting to know whether the circulating insulin levels varied in the anticipated manner.

The authors hypothesize that the excess lactate produced in the burned limb results from shunting of an excess of pyruvate that exceeds the capacity of pyruvate dehydrogenase activity and that that relative enzyme deficiency can be exaggerated by bacteremia.

In light of that, I ask Dr. Gore whether he measured pyruvate dehydrogenase activity in any of the limbs that were studied and whether any of the patients had bacteremia.

Alternatively the authors consider the possibility that beta blockade diminishes lactate production by inhibiting lypolysis. That possibility would be supported if data are available documenting that propanolol administration was associated with a decrease in plasma-free fatty acids.

A methodologic concern exists as well. Because oxygen consumption and respiratory quotient were not influenced by the propanolol dosage used, one might ask whether adequacy of the beta adrenergic blockade was assessed by confirming a failure of heart rate to increase and serum-free fatty acids to increase after an intravenous isoproterenol challenge.

As is often the case, a perturbation of the postinjury physiologic milieu that benefits one system may have untoward effects on others. As Dr. Gore noted, in an earlier study of patients who received propanolol infusions for 5 days, this group found that urea production increased, suggesting that a greater erosion of lean body mass occurred with such therapy, and that might only serve to prolong convalescence. I also wonder whether the observed changes in limb blood flow and metabolism would delay the healing of wounds on the limbs.

On the basis of their findings, the authors suggest that hormonal manipulation can be used to reduce metabolic stress and cardiac work in burn patients. And that is a most attractive potential means to simplify metabolic support of hypermetabolic burn patients in general and reduce cardiac stress in burn patients with limited cardiac reserve in particular.

DR. DONALD GANN (Baltimore, Maryland): I would like to ask the authors two questions that do not carry with it the philosophic significance of those of the other discusssants, but I am a little confused by some of the physiology.

First they report that after beta blockade there is increased epinephrine. I can understand that because decrease in cardiac force and in heart rate would be expected to result in stimulation of the baroceptor reflex and increased epinephrine production. But they note a decrease in norepinephrine and that flies in the face of what little we know about catecholamine physiology. I was wondering just how they might explain that, unless perhaps the plasma levels do not reflect what is going on in the adrenal medulla or the nerve endings, in which case the whole question of what the study means is raised.

The other issue has to do with the finding of decreased lactate production. It seems to me that when you have a decrease in blood flow, you clearly have a decrease in lactate appearance. But to infer a decrease in production in the face of decreased flow, you must show that the decreased appearance was out of proportion to what you might expect as the product of the flow and the constant production rate. I did not hear that in the presentation.

DR. DENNIS GORE (Closing discussion): I will address Dr. Ward's comments first. The general notion of giving beta blockers to burn patients is related to their accelerated hyperdynamic state.

This is most detrimental to the elderly patients in whom cardiac reserve is somewhat limited. So we would, in theory, be more likely to give these beta blockers to those patients who could not tolerate the accelerated heart rate, and so forth. Those patients are prone to cardiac decompensation and beta blockade may be most useful in that subset of patients.

He also commented on the correlation of blood flow and metabolic response to the percentage of leg burn. As was well shown by Dr. Wilmore more than 10 years ago, the percentage of leg burn correlates with an increase in leg blood flow. Our study did not show this association because most of our patients were severely burned and we used all available skin for donor site. So we created an open wound on the leg that was rather proportional in each patient. And that is probably why we did not see any changes in blood flows because we had proportionately similar open wounds.

None of these patients were septic or bacteremic. There were no febrile responses during the study, and blood cultures around this period of study were negative for identifying organisms.

Dr. Ward also asked about the efficiency of using beta blockade in that it may supply the energy substrates to the wound since the total body energy expenditure was about the same, with and without Propranolol. It may be that beta blockade is not decreasing the energy substrate delivery but just altering substrate oxidation so the efficiency of pyruvate oxidation is increased.

Dr. Pruitt asked whether we measured pyruvate dehydrogenase enzyme activity. We did not. It would have been an excellent additive measurement. We also unfortunately did not measure free fatty acid levels.

Dr. Pruitt also asked about the increased urea production noted with beta blockade as reported in a previous study from the Galveston Shriners' Hospital—that was a chronic study in which we gave beta blockers during a minimum period of 5 days and then measured urea production and cardiac performance. We showed that urea production was elevated in the patients receiving beta blockade. In this acute study we were not able to demonstrate an increased urinary nitrogen loss with the beta blockade. We showed that blood flow to the leg was reduced with beta blockade. Intuitively, one can suggest that if you have a prolonged decrease in blood flow to an extremity, over time this may result in increased muscle catabolism.

Finally Dr. Gann asked about the change in epinephrine levels. The increase in epinephrine with beta blockade is a documented phenomenon, however I and others have been unable to offer an explanation.

Dr. Gann also asked if the alterations in leg blood flow were considered in calculating lactate production. Blood flow was used in determining the substrate net balances in this study.

Prophylactic Use of High-frequency Percussive Ventilation in Patients with Inhalation Injury

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Death and the incidence of pneumonia are significantly increased in burn patients with inhalation injury, despite application of conventional ventilatory support techniques. The effect of high-frequency percussive ventilation on mortality rate, incidence of pulmonary infection, and barotrauma were studied in 54 burn patients with documented inhalation injury admitted between March 1987 and September 1990 as compared to an historic cohort treated between 1980 and 1984. All patients satisfied clinical criteria for mechanical ventilation. High-frequency percussive ventilation was initiated within 24 hours of intubation. The patients' mean age and burn size were 32.2 years and 47.8%, respectively (ranges, 15 to 88 years; 0% to 90%). The mean number of ventilator days was 15.3 ± 16.7 (range, 1 to 150 days), with 26% of patients ventilated for more than 2 weeks. Fourteen patients (25.9%) developed pneumonia compared to an historic frequency of 45.8% ($p < 0.005$). Mortality rate was 18.5% (10 patients) with an expected historic number of deaths of 23 (95% confidence limits of 17 to 28 deaths). The documented improvement in survival rate and decrease in the incidence of pneumonia in patients treated with prophylactic high-frequency ventilation (HFV), as compared to a cohort of patients treated in the 7 years before the trial, indicates the importance of small airway patency in the pathogenesis of inhalation injury sequelae and supports further use and evaluation of HFV.

DURING THE PAST three decades, improvements in burn wound management, infection control, and metabolic support increased the survival of thermally injured patients. Inhalation injury, however, continues to be a significant comorbid factor in such patients, and its treatment has been improved little by the use of conventional means of pulmonary support. Bacterial pneumonia, which historically occurred in 38% of all patients with inhalation injury but in only 8% of those without such injury, continues to be the leading cause of morbidity and death. The combination of inhalation injury and pneumonia exert independent but additive effects on the age-related death attributable to burn size.[1]

Current treatment for inhalation injury is supportive and includes aggressive pulmonary toilet, mechanical ventilatory support when indicated, and aggressive treatment of pneumonia when diagnosed. In an ovine model, we showed that the major insult after smoke injury (as indexed by early postinjury ventilation/perfusion (VA/Q) mismatching and histopathologic findings) is the obstruction and collapse of small airways leading to distal atelectasis and subsequent pneumonia.[2] Experimental and clinical data suggest that high-frequency ventilation (HFV) may be beneficial in recruiting and stabilizing such collapsed diseased lung segments.[3-12] In addition some investigators reported improved clearance of secretions from the tracheobronchial tree with the use of HFV.[13] These observations support the hypothesis that HFV, by preventing alveolar collapse and improving secretion clearance, may be beneficial in patients with inhalation injury.

We previously reported a small cohort of 10 patients with inhalation injury requiring mechanical ventilatory support in whom the prophylactic use of high-frequency percussive ventilation (HFPV) appeared to reduce the incidence of pneumonia.[14] This report extends our observations to 54 patients in whom HFPV was used in a prophylactic manner in an attempt to decrease the incidence of pneumonia and improve survival rate.

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The views of the authors do not purport to reflect the positions of the Department of the Army and the Department of Defense.

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Methods

Patient Population

All adult patients admitted to the United States Army Institute of Surgical Research between March 1987 and September 1990 with a diagnosis of inhalation injury were eligible for enrollment in this study. Inhalation injury was confirmed in each patient by bronchoscopy and/or^{133} Xenon ventilation–perfusion lung scan. The presence of carbonaceous debris beneath the true vocal cords, mucosal erythema, and ulceration were used to define moderate to severe inhalation injury. Patients with a positive^{133} Xenon scan and negative bronchoscopy were determined to have mild inhalation injury. These criteria were established in our earlier review.[1] After meeting the entrance requirements listed in Table 1 and meeting the requirements for intubation and mechanical ventilatory support listed in Table 2, informed consent was obtained from each patient and HFPV initiated for pneumonia prophylaxis.

High-frequency Percussive Ventilation

Description of the high frequency percussive ventilator used in this study has been published.[14] Briefly, HFPV was delivered by a high-frequency pulse generator with gas from the high-frequency pulse generator delivered through a nongated sliding venturi to a standard endotracheal tube. The venturi entrains humidified gas from a fresh bias gas flow provided from the ventilator. The system combines serial high-frequency sub-dead space volume breaths with a variable inspiratory:expiratory (I:E) ratio. Periodic interruption of the high-frequency pulsatile flow is programmed to allow return of airway pressure to baseline continuous positive airway pressure (CPAP). The duration of the percussive phase and of the return to baseline phase are adjusted to manipulate oxygenation and CO_2 elimination. Peak airway pressure also can be varied independently to maintain CO_2 clearance. The frequency of sub-dead space breaths can range between 1.5 and 15 hertz. FIO_2 and PEEP are adjusted to maintain O_2 saturation greater than 90%.

All patients were placed initially on a conventional mechanical ventilator. In those patients intubated elsewhere, such support was of less than 24 hours duration, and all patients were converted to HFPV within 1 hour of admission. The patients intubated at our institution received conventional ventilation during admission processing but were converted to HFPV within 1 hour. After placing the patient on HFPV, standard ventilator settings were used as a baseline and then altered as indicated by arterial blood gas determinations, pulse oximetry, and end tidal CO_2 monitoring. The duration of the percussive phase was set at 2 seconds, with a rate of return to baseline approximately 2 less than the intermittant mandatory ventilation (IMV) setting required to maintain normal acid-base balance on conventional mechanical ventilation. Peak airway pressures were set at 5 cm H_2O less than those developed when a conventional volume-limited ventilator was set to deliver a tidal volume of 12 to 15 mL/kg. The FIO_2 and PEEP were maintained initially at the same levels as on conventional mechanical ventilation. The frequency of the sub-dead space tidal breaths was initially set at 10 hertz. After stabilization for approximately 30 minutes, arterial blood gas measurements were obtained and adjustments made as indicated. The goal of ventilator therapy was to maintain oxygenation and ventilation at the lowest possible peak airway pressure and fractional inspired oxygen concentration. Patients were weaned and extubated according to standard criteria.

TABLE 1. *Study Entrance Criteria*

Inhalation injury documented by bronchoscopy or Xenon lung scan
Clinical requirement for ventilatory support
Admission within 48 hours of injury
Older than 15 years

TABLE 2. *Requirements for Mechanical Ventilatory Support*

1. Respiratory rate > 35/min
2. Vital capacity < 15 mL/kg
3. Inspiratory force < 25 cm H_2O
4. $PAO_2/FIO_2 < 200$
5. $PCO_2 > 50$ mmHg
6. $Vd/Vt > 0.6$
7. Upper airway edema
8. $PCO_2 < 50$ mmHg but progressively increasing
9. Increased work of breathing

Diagnosis of Pneumonia

The diagnosis of pneumonia was based on standard criteria used in this institution for the past decade. Patients with sputum leukocytosis (more than 25 white blood cells per high-power field), lack of oropharyngeal contamination (less than 10 squamous cells per high-power field), a predominant organism on culture, and an infiltrate on chest roentgenograms were diagnosed as having pneumonia.

Data Analysis

The incidence of pneumonia and death in the study patients was compared with predicted values based on two previous studies. The first predictor used relates burn size and age to death for all patients admitted to the Institute of Surgical Research between January 1980 and December 1986. The second predictor used as a basis for comparison relates burn size, age, the presence of inhalation injury and the occurrence of pneumonia to death

TABLE 3. *Burn Mortality Predictors*

$$\text{Predicted Mortality (PM)} = \frac{e^Y}{1 + e^Y}$$

I. Logistic equation relating burn size and age to mortality: 1980–1986

$$Y = -4.8216 + 0.10299\,(\text{PCTB}) - 0.18879\,(\text{Age}) + 0.50873\,(\text{Age}^2/100) - 0.27915\,(\text{Age}^3/10{,}000)$$

II. Logistic equation relating burn size, age, inhalation injury, and pneumonia to mortality: 1980–1984

$$Y = -3.4953 + 0.09589\,(\text{PCTB}) - 0.1988\,(\text{Age}) + 0.4478\,(\text{Age}^2/100) - 0.20314\,(\text{Age}^3/10{,}000) + 0.59056\,(\text{II}) + 0.92530\,(\text{PNeu})$$

PCTB, percentage of total body surface burned.
II = −1.0 if inhalation injury absent; +1.0 if inhalation injury present.
PNEU, −1.0 if pneumonia absent; +1.0 if pneumonia present.

in patients admitted between 1980 and 1984. The incidence of pneumonia in this latter patient population also was used for comparison purposes. Solution of the logistic equations listed in Table 3 provide the exponents for use in calculating the two values for predicted death.

Results

Patient Population

Fifty-four patients meeting the entrance criteria were enrolled in the study. Routine demographic data are included in Table 4. Ten patients died, for a mortality rate of 18.5%. The distribution of patients by burn size demonstrates that 50% of the patients had burns ranging between 30% and 60% of the body surface, which is the group of patients in whom inhalation injury has been reported to have its greatest impact on death (Fig. 1). Segregation of the patients by outcome revealed the expected differences between the two groups (Table 5); nonsurvivors were older and had larger burns and a greater incidence of pneumonia. Fifty-two of the fifty-four patients were diagnosed as having inhalation injury by bronchoscopy. The two patients with negative bronchoscopy but positive ^{133}Xenon scans developed severe adult respiratory distress syndrome (ARDS) in the first postburn week, necessitating mechanical ventilatory support.

TABLE 4. *Demographic Data*

Age	32.2 ± 1.8 (15–88)*
TBSB	47.8 ± 3.1 (0–90)
Sex	40 male, 14 female
Days on ventilator	15.3 ± 2.2 (1–150)
Bronchoscopy positive	96.3%
Incidence of pneumonia	25.9%
Mortality	10/54 (18.5%)

* X ± SEM (range).
TBSB, total body surface burn.

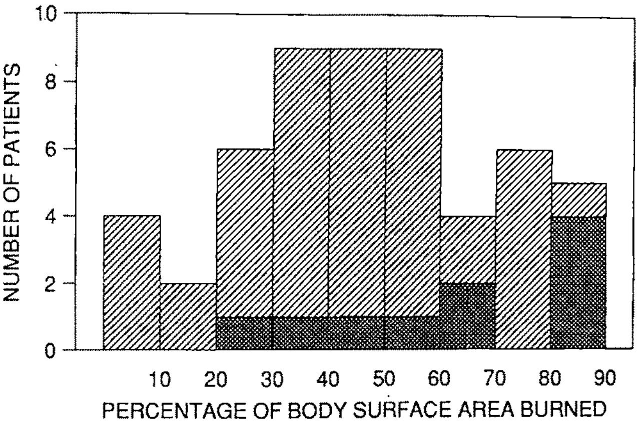

FIG. 1. Distribution of burn size for the 54 patients in the study. Of note is that 50% of the patient burn sizes are between 30% to 60% of the body surface area, which is the group of patients in whom inhalation injury exerts its greatest influence on mortality. Survivors are reported by the crossed bars, and nonsurvivors by the crosshatched bars.

Historically 45.8% of patients with positive bronchoscopy and 19.5% of patients with negative bronchoscopy but a positive ^{133}Xenon lung scan developed pneumonia. Based on that experience, 25 of the study patients would have been expected to develop pneumonia during hospitalization. Pneumonia was diagnosed in only 14 (26%) of the patients in this study, an incidence differing significantly from that of the comparison cohort ($p < 0.003$).

Actual Versus *Predicted Death*

Ten deaths occurred in this group of patients, for an observed mortality rate of 18.5%. To determine whether HFPV influenced outcome in this group of patients, we compared this observed mortality rate with two mortality predictions generated from patient data from this institution, as noted above. The first, based on burn size and age, related death in all patients admitted to this institution between January 1980 and December 1986, predicts the deaths of 19 patients (35%) in the study population, with a 95% confidence interval of 13 to 25 deaths. The second, based on burn size and age, related death in conjunction with the additive effects of inhalation injury and pneumonia and generated from patient data between January 1980 and December 1984, predicts 23 deaths (42.6%) with

TABLE 5. *Comparison of Survivors and Nonsurvivors*

	Survivors	Nonsurvivors	
Age (years)	29.6 ± 1.5*	43.3 ± 6.5	$p < 0.05$
TBSB	43.7 ± 3.2	65.3 ± 7.1	$p < 0.01$
Incidence of pneumonia	20.5%	50%	$p < 0.05$

* Mean ± SEM.
TBSB, total body surface burn.

a 95% confidence interval of 17 to 28 deaths. Thus the mortality rate in this cohort of patients was significantly less than that predicted by either technique ($p < 0.05$) (Table 6).

The causes of death in those patients who died are listed in Table 7. Of the 10 deaths, four were from pulmonary failure. One patient could not be ventilated and oxygenated and was changed to conventional ventilatory support with the same result. Three patients developed progressive pulmonary failure and died on postburn days 12, 43, and 50, respectively. Of the remaining 6 patients, 2 were resuscitation failures who died with severe inhalation injury, 1 patient extubated himself on postburn day 7 and died of cardiopulmonary arrest despite an emergency tracheostomy, and 1 patient was removed from the study by his attending surgeon. Two patients died from cerebrovascular accidents after they were extubated for 30 and 45 days, respectively.

Ventilator complications were rare. Two patients developed severe necrotizing tracheobronchitis. It could not be determined whether this was secondary to the ventilator or the disease process itself. Barotrauma occurred in three patients. Two developed significant subcutaneous emphysema and one patient developed bilateral pneumothoraces requiring tube thoracostomies.

Discussion

The combination of cutaneous thermal injury and inhalation injury results in a significantly higher mortality rate than that attributable to cutaneous thermal injury alone. This additive effect of inhalation injury on death is most apparent in patients in whom predicted mortality attributable to age and burn size ranges from 40% to 60%. Inhalation injury also results in a marked increase in the incidence of bacterial pneumonia. As previously stated, only 8.8% of patients with thermal injury but without inhalation injury develop pneumonia during their course of treatment. The presence of inhalation injury, whether diagnosed by bronchoscopy or ^{133}Xenon scan, historically resulted in a 38% incidence of pneumonia, and the combination of inhalation injury and pneumonia has an even more drastic effect on outcome, increasing the mortality rate by as much as 60%.[1]

TABLE 6. *Actual* Versus *Predicted Outcome*

Predictor	Predicted Deaths	95% CL	Observed
#1 (1980–1986)	19	13–25	10
#2 (1980–1984)*	23	17–28	10

* This predictor includes the impact that inhalation injury and pneumonia have on outcome.

CL, confidence level.

TABLE 7. *Cause of Death*

TBSB (%)	Age (years)	PBD	Cause of Death
90	32	01	Resuscitation failure
85	25	03	Resuscitation failure
59	40	07	Accidental extubation
36	59	40	Removed from study
47	29	50	SBE, CVA, 30 days after extubation
65	60	80	CVA, 45 days following extubation
89	25	12	Pulmonary failure
30	88	43	Pneumonia (*Staph. aureus*), pulmonary failure
64	49	01	Unable to ventilate
86	29	50	Pneumonia, Aspergillus wound infection

TBSB, total body surface burn; PBD, postburn day.

Ideally the optimal treatment of any disease should reverse the pathophysiologic process without causing further injury. When inhalation injury is severe enough to require conventional mechanical ventilatory support, such an outcome is not achieved. The pathophysiologic response to inhalation injury includes extensive tracheobronchial injury, which results in sloughing of the mucosal lining of the respiratory tract and leads to obstruction of small- and moderate-sized airways. In addition, the mucociliary transport mechanism is impaired, resulting in impaired clearance of secretions and the sloughed debris. Distal airway obstruction results in atelectasis and, in conjunction with the disruption of the endothelial and epithelial integrity of the alveolus, produces foci for the development of bacterial overgrowth and subsequent pneumonia. The combination of atelectasis, pneumonia, and airway obstruction produces significant derangement of ventilation–perfusion relationships.

Conventional mechanical ventilatory support does not reverse these processes, is not characterized by improved clearance of secretions, and may actually compound the existing injury.[15] Conventional volume-limited ventilation in patients with inhalation injury normally is instituted at a tidal volume of 12 to 15 mL/kg. With such a ventilatory setting, peak inspiratory pressures often are elevated during the resuscitative and fluid mobilization phase of care. Recently Tsuno[16] reported adverse pulmonary effects of volume-limited mechanical ventilation when peak inspiratory pressures exceed 30 cm of water in paralyzed, anesthetized healthy sheep. Animals ventilated with an FIO$_2$ of 40% and a tidal volume of 10 mL/kg, with peak inspiratory pressure less than 18 cm of water, showed no measurable deleterious changes in lung function or histopathology after 48 hours of support. Animals ventilated with larger tidal volumes, resulting in peak inspiratory pressures greater than 30 cm H_2O, demonstrated progressive deterioration in static lung compliance, functional residual capacity, and arterial blood gases. Severe pulmonary atelectasis, increased wet lung weight, and an increase in the minimum surface tension of saline lung lavage fluid were noted at autopsy. These data indicate that even in normal healthy lungs, prolonged elevation of inspiratory pressures may result in injury.

If pneumonia develops after resuscitation, the requirement for increased inspired oxygen concentrations to achieve normoxia may result in increased pulmonary damage when infection is present. Coalson et al.[17] recently reported a synergistic effect of hyperoxia and infection resulting in significant pulmonary dysfunction and damage. In a primate model, the combination of 80% O_2 and Pseudomonas pneumonia was as injurious as 100% oxygen during an 11-day period, while 80% O_2 or pneumonia alone resulted in minimal dysfunction.

The reported beneficial effects of HFV (ventilator frequency greater than 60 breaths/minute and tidal volumes of less than anatomic dead space) include lower peak airway pressures than those generated by conventional ventilation, positive endotracheal pressure throughout the ventilatory cycle, increased functional reserve capacity, and more efficient pulmonary gas distribution.[18] Unfortunately each of the advantages claimed for specific high-frequency ventilators has been refuted in various reports.[9,10,12] If, however, a form of HFV could achieve some of these advantages and maintain oxygenation and CO_2 clearance at lower inspiratory pressures and fractional inspired concentrations of oxygen, it might be possible to provide ventilatory support and avoid the deleterious side effects of conventional support.

In evaluating clinical reports of HFV, the physician must recognize that there are several types of high-frequency ventilators, all with different characteristics and different potentially adverse effects. Furthermore one must differentiate between prophylactic use of the ventilator, as in this study, and therapeutic or salvage use of the high-frequency device for patients in whom conventional mechanical ventilatory support has failed. Many reports documented the effectiveness of short-term salvage use of HFV in patients with ARDS.[7,8] Our own previously reported experience demonstrated that the ventilator used in these studies could oxygenate and ventilate patients at lower airway pressures and inspired oxygen concentrations, but all the patients died despite improved pulmonary performance.[14] Other reports also failed to identify a survival advantage with the use of HFV as a salvage mode of ventilatory support.

In this study we used HFPV prophylactically in an attempt to avoid the adverse effects of mechanical ventilatory support while reversing or minimizing some of the pathophysiologic changes that occur after inhalation injury. Our data indicate that, as compared to a recent historic cohort, the use of HFPV resulted in a significant decrease in the incidence of pneumonia and a decrease in the number of deaths.

There are several problems inherent to the use of historic controls. The development of more sensitive diagnostic techniques resulting in the diagnosis of less severe injury could favorably bias the results of recent studies, although the diagnostic modalities and criteria have remained constant since 1976. It is generally accepted that during the past three decades, survival of all patients with thermal injury has improved. Even so the effects of inhalation injury and pneumonia on outcome have remained refractory to standard treatment, as indicated by the mortality predictor used at this institution. Furthermore the predictors used in this study introduce some bias against finding an improvement in outcome in the current study population as compared to the populations on which the predictors were based. The predictor that account for the effects of both burn size and age as well as pneumonia and inhalation injury on death was based on all patients with inhalation injury admitted during the years 1980 to 1984, regardless of whether they required mechanical ventilatory support. The present study population includes only the sickest patients with the most significant injuries, all requiring ventilatory support. Demonstration of a survival advantage in this group of patients compared to a group that included patients with less severe injury supports the hypothesis that HFPV has a significant, beneficial effect. In short it seems reasonable to assign a major portion of the decrease in incidence of pneumonia and improvement in outcome of the study patients to the ventilatory support used.

Only two other published studies in the literature evaluated the prophylactic use of HFV in patients requiring ventilatory support as prophylaxis against ARDS. In 1986 Carlon[18] reported a study of 309 patients who were randomized to high-frequency jet ventilation or conventional ventilatory support. All patients who were admitted to the intensive care unit and who were at risk for the development of pulmonary failure were entered into the study. The use of high-frequency jet ventilation resulted in lower peak airway pressures but did not decrease the 4% incidence of barotrauma or improve the overall outcome as compared to conventional support. In 1990 Hurst et al.[19] reported a study of 113 patients at risk for the development of ARDS who were randomized to receive ventilatory support with HFPV or conventional mechanical ventilation before the onset of ARDS. Changes in ventilator settings were made to achieve the same therapeutic endpoints in both groups of patients. There was no difference in the percentage of patients who developed ARDS in either group. In the patients who developed ARDS, HFV achieved therapeutic endpoints at lower peak airway pressures, lower positive end expiratory pressures, and an increased inspiratory time as compared to the conventional group. There was, however, no difference in the incidence of barotrauma or outcome in those patients. Both of these studies involved heterogeneous patient populations, in which the etiology of respiratory failure was diverse, usually a consequence of a systemic insult that resulted in diffuse parenchymal disease and dysfunction. This type of insult is quite distinct from that seen after smoke inhalation in both humans and animal models, in which edema resolves rapidly after resuscitation and repair of the airway mucosa typically occurs within 14 to 21 days.

The exact mechanism by which HFPV achieved the results reported in this study is not known. We hypothesize that the ability to maintain ventilation and oxygenation at lower peak airway pressures and inspired oxygen concentrations may decrease the iatrogenic injury that occurs with conventional mechanical ventilatory support. Extrapolation of the data reported by Tsuno[16] to humans would indicate that ventilation at lower peak airway pressures offers significant advantage, especially in lungs that have already been injured. In addition several studies now suggest that asymmetric high-frequency breaths improve clearance of secretions, results that have been obtained with high-frequency jet ventilators and high-frequency oscillators, both *in vitro* and *in vivo*.[13,20-22] Our clinical experience supports this finding. Patients with severe inhalation injury treated prophylactically with high-frequency percussive ventilation typically are found, by bronchoscopic examination, to have large deposits of secretions at the tip of the endotracheal tube. After removal of these secretions, the main stem bronchi and distal airways often are patent and free of pathologic secretions. The documented improvement in survival and the decrease in the incidence of pneumonia in patients treated with prophylactic HFPV, as compared to the recent historic cohort, indicate the importance of maintaining small airway patency in reducing the sequela of inhalation injury. The beneficial effects reported here and the paucity of ventilator complications support continued use and further evaluation of HFV in patients with inhalation injury.

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DISCUSSIONS

DR. HARVEY SUGERMAN (Richmond, Virginia): In this study, high-frequency percussive ventilation from 1987 through 1990 was associated with a significant decrease in, one, the incidence of pneumonia and, two, the mortality rate when compared, as mentioned, to historical controls for inhalational injury from 1980 through 1984 and mortality rate from 1980 through 1986.

As discussed in their paper, this is one of the only studies in which high-frequency ventilation has shown a significant decrease in mortality rate. It has been my experience and that of the literature that you can significantly, but only temporarily, improve blood gas parameters in ARDS patients with high-frequency ventilation. It prolongs death rather than improving survival.

The hypothesis proposed by Dr. Cioffi and his colleagues and supported by sheep inhalational injury studies in their laboratory is that high-frequency percussive ventilation improves bronchiopulmonary toilet of the small airways, which are plugged with soot and debris, with an increased alveolar recruitment and ventilation at lower peak airway pressures when high-frequency ventilation is provided early or prophylactically before the development of severe ARDS.

This has not been the case in nonburn septic patients in randomized prospective trials. Dr. Cioffi's study suffers from all of the potential weaknesses of a nonrandomized trial. In comparing inhalational injury and the risk of pneumonia, why did the authors compare data from 1980 to 1984 with 1987 to 1990?

What happened to the missing 3 years? Were other treatment modalities that could influence the development of pneumonia during these two time intervals changed, such as the use of H2 blockers *versus* carafate for the prevention of stress ulcers or TPN *versus* enteral feedings vis-a-vis the issue of bacterial translocation, and so on?

Were the methods of providing pulmonary toilet in the two groups, such as the nursing staff and inhalational therapists, unchanged during these two time periods?

Could prejudice have been inadvertently present in roentgenographic interpretation or were so-called blinded radiologists used to describe the presence or absence of pulmonary infiltrates?

Finally, using historical controls, were there any differences in the duration of mechanical ventilation *versus* duration of ventilation with high-frequency ventilation present?

We heard the duration of ventilation for high-frequency ventilation but not for the mechanical ventilatory group.

In 1988 this group reported their first positive experience with high-frequency percussive ventilation in 14 patients before the American Association for the Surgery of Trauma. Today we have heard more suggestive data in an additional 40 patients.

High-frequency ventilation has been a technique in search of documented therapeutic efficacy. Now is the time for a truly randomized prospective, perhaps multi-center trial for the study of high-frequency ventilation in burn inhalational injury patients.

DR. DAVID HERNDON (Galveston, Texas): Dr. Cioffi and Dr. Pruitt and their group must be commended on their impressive mortality statistics. A mortality rate as low as 18.5% in a group of patients with significant inhalation and burn injury requiring prolonged ventilatory support has never been reported in the United States before.

The usual mortality rates quoted are from 40% to 50%. This in respect to nationally reported mortality rates is clearly a great advance and allows Brooke still to be called the world's most famous burn unit.

However demonstration of a treatment effect in a patient population with this high rate of mortality is extremely difficult. Comparison to an historic cohort from 1980 to 1984 or 1986 is somewhat misleading. The investigators have admitted that.

I would like to know if more aggressive early surgical removal of the burn wound in a later period may have contributed to a decrease in the incidence of pneumonia by decreasing burn wound bacteremia as a source of hematogenous pneumonia. Has there been any effect of the more recently developed antibiotics?

The H2 blockers have been mentioned.

You have noted also that a wide variety of high-frequency ventilators are available, and varying reports of efficacy in the literature have been received. The incidence of barotrauma, specifically pneumothoraces due to gas trapped behind inspissated mucosal casts, has been discouraging in inhalation injury patients. However the ventilator you used is very specific and seems to overcome many of these adverse effects with a very low incidence of barotrauma.

My major question is, is this complicated ventilator commercially available or will it become commercially available? I'm not aware of it being so. If it is, then I think, as Dr. Sugerman did, concurrent multicenter studies based on your encouraging preliminary results might be warranted to determine mortality effects, whether specific for this machine or specific for this excellent treatment team.

I would also like the authors to speculate as to whether our general level of burn care has improved to such an extent that we might also recontemplate randomized studies that would treat barotrauma by use of extracorporeal membrane oxygenation.

Previous attempts in the 1970s, when burn wound sepsis was rampant, were unsuccessful, but mortality statistics are sufficiently decreased, and early excision of the wound would prevent many of the septic complications that were seen before. Or perhaps the new technique of intravenacava filamentous O_2–CO_2 exchange rods being tested in multiple centers for support of adult respiratory distress syndrome might make more sense than a jet ventilator.

DR. EDWIN DEITCH (Shreveport, Louisiana): I will limit my remarks to a few questions, some of which have been covered before but, nonetheless, I think they need to be stated again.

I wonder whether the authors are now ready to carry out a prospective randomized study to verify these results. There are several reasons to do so. The first is that this high-frequency ventilator technique that they are proposing is much more time consuming, technically demanding and more expensive than conventional mechanical ventilation.

And second, and perhaps more important, all too often in the past studies carried out using historical controls, even one as well defined as this one, fail to verify the encouraging results of the initial study.

There are many reasons why this phenomenon occurs, not the least of which is the special attention directed toward these patients by a highly motivated investigational team. Perhaps the fact that Dr. Cioffi and his coworkers were performing bronchoscopy on these patients to remove debris may have made this a study of repeated bronchoscopy as much as ventilatory support.

I have two other related questions. One is that it has become apparent in the last several years that the intubated patients receiving antacids or H2 blockers for stress ulcer have an increased incidence of gram-negative pneumonia and even death.

Therefore I wonder whether the authors are still using H2 blockers, what they're using, and whether they have changed their therapy to use sucralfate to prevent colonization of the stomach with potential pathogens.

Related to that, do you have any data on the bacteriology in these patients and if so was it different from the historical controls? I ask this question because pneumonia due to gram-negative enteric bacilli or pseudomonas is associated with a higher mortality rate than pneumonias caused by gram-positive organisms.

Therefore, if you are shifting your flora due to changes in therapy, you may also be shifting your results.

DR. ANTHONY MEYER (Chapel Hill, North Carolina): I would like to compliment the authors on their continued evaluation of this alternate method of ventilation for inhalation injury. I have a few questions.

You had a relatively low incidence of necrotizing tracheobronchitis and barotrauma. Is this consistent with the incidence in your conventionally ventilated patients?

Is there any evidence or data on pulmonary compliance in these patients? Obviously it is difficult to measure using this mode of ventilation, but if pulmonary fibrosis is one of the key hallmarks of ARDS and late pulmonary problems, and if this is indeed triggered by the barotrauma of conventional ventilation, this might be a significant physiologic alteration using this type of support.

There is a relatively high incidence of pneumonia in the historical series. And because of this and many of the other reasons, I would like to join the chorus in suggesting that a true prospective randomized study should be carried out to evaluation further the technique.

I think it is interesting that this sophisticated pulmonary management is being discussed before a surgical society rather than something that is only discussed before pulmonary medicine groups.

DR. WILLIAM CIOFFI (Closing discussion): First I would like to address the recurring question of why we did not perform a randomized trial.

When we started this study, we did a trial in which we enrolled 20 patients to see if we could see a decrease in the incidence of pneumonia or change in mortality rate, and indeed we did. We entertained the thought of a prospective randomized trial at that time. By doing the calculations, we discovered that it would require more than 230 patients to have satisfactory type one and type two errors. It took us almost 4 years to enroll 54 patients in this trial, so we were looking at more than a decade to complete the study with all the problems that would occur in treatment changes in 10 years or more.

Second we have used these predictors for at least one decade in our institute, if not longer, and in other studies have found them to be entirely reliable in predicting results from other types of studies, not just including the ventilator study discussed here today.

Third because doing this randomized trial will be difficult in a period of time that is reasonable, we have begun a study in primates looking at high-frequency ventilation in two forms, high-frequency percussive ventilation discussed here today and high-frequency oscillation as compared to conventional ventilation in a long-term support model in which we ought to be able to discern whether the differences we see in patients will hold out in the primate model. That trial is now underway.

To continue with Dr. Sugerman's questions, other treatment modalities have not changed significantly in our unit in the past 10 years.

Our mode of nutritional support is enteral and has remained enteral for 10 years, with TPN being used in less than 5% of patients.

Our diagnosis and treatment of pneumonia also has remained the same in the studied period of 10 years.

Respiratory therapy has not changed significantly. Frequent bronchoscopy for pulmonary toilet in patients with severe inhalation injury has been the standard in the unit for approximately 10 to 15 years.

Dr. Sugerman also asked whether the duration of ventilatory support was similar in the high-frequency patients as compared to the conventional patients. Unfortunately I do not have that data for the 1980–1984 patients. But I would say that 15 days of support in these patients indicates a rather severe insult. The patients are weaned as quickly as possible from this ventilator, and it has been my experience in patients who have not been placed in the trial for other reasons that it is easier to wean the patients from high-frequency ventilation than conventional support.

Dr. Herndon asked about our excision practices. In the past decade, our day of first excision has decreased by about 3 days in patients with burn size discussed in this paper. He also asked whether the incidence of hematogenous *versus* bronchopneumonia or airway pneumonia has changed. Hematogenous pneumonia has been relatively infrequent in the past decade, and bronchopneumonia is responsible for almost all our pneumonias. I don't think that later excision in the earlier group had much to do with the incidence of pneumonia.

Our antibiotic therapy has been relatively unchanged. The standard antibiotic therapy in our unit is Amicacin and Vancomycin and has been that way for almost the entire period of the 1980s.

Several discussants asked about stress ulcer prophylaxis and whether we use H2 blockers. Until 5 or 6 months ago the standard of care was H2 blockers and antacids titrated to keep the gastric pH above 4.5.

We just started a trial comparing sucralfate to standard therapy, but of the patients reported in this study, only two of the last five patients were enrolled in that study. So all patients were on H2 blockers, and the idea of nonacid neutralizing therapy to decrease pneumonia does not enter into play.

The barotrauma reported in our series is low. It is lower than it has been in the past. The incidence of significant barotrauma as far as pneumothoraces was one patient of 54. Most ICUs report incidence of barotrauma approximately 4%. Two patients did have significant subcutaneous emphysema but never developed a pneumothorax.

Dr. Herndon asked whether this device was commercially available. It was approved by the FDA approximately 1 year ago and is now commercially available through Percussion Air Corporation, which is a company owned by Dr. Bird, who developed this form of ventilation.

Dr. Herndon also asked us to speculate whether other forms of support, total rest of the lungs using either ECCOR or the new intravenacaval device, the IVOX, might be of more benefit. In those studies it is still a requirement that the patient be kept on high mean airway, low peak pressure ventilation to splint the lung. And it might be that some high-frequency ventilation in combination with extracorporeal support might be the answer. The studies that are using that form of therapy, however, are all on ARDS patients.

Dr. Deitch asked not only about why not a prospective study, which I've already covered, but also about the costs. The cost of this ventilator is approximately one fifth of a 7200 ventilator. So cost is not really an issue.

The first two forms of this ventilator were exceptionally hard to use, as we reported in our early review; however the VDR for the most current form of this ventilation is very easy to use. We have residents who rotate 1 month from multiple institutions. And by the end of 1 month, most residents are capable of using this ventilator and are able to support the patients at night on their own.

Dr. Deitch also asked about the etiology of our pneumonia, our gram negatives *versus* gram positives. We have had a predominance of gram-positive pneumonias at our institute for more than a decade, and that incidence has not changed.

He also asked about comparing it to a population from 1980 to 1984 and 1987 to 1990. We are just starting to look at the data in the intervening years. And the incidence of pneumonia before use of this ventilation from 1985 to 1987 had not changed in patients with inhalation injury compared to the 1980 to 1984 group.

Finally Dr. Meyers asked about necrotizing tracheobronchitis. It is our impression that it has been significantly decreased with the use of this ventilator, despite the fact that there are reports in the literature using this form of ventilation in neonates, in which that incidence approaches one third to one half of patients.

However we only had two patients, the very first patient and a latter patient entered in the trial, both of whom survived. And it appeared to be more an indication of the severity of their insult.

Finally, Dr. Meyers, we have not done compliance measurements to indicate the severity of the insult.

In closing I would like to add that many discussants compared this form of support in patients with inhalation injury to those studies in the literature that deal with ARDS patients. I would emphasize that the insult in our patients is distinctly different from ARDS. It is a self-limiting disease process, which, if it can be left to heal on its own, should do so in 10 to 14 days. We feel strongly that conventional mechanical ventilatory support impairs that healing process and that the use of low-pressure ventilation by the use of this device or other high-frequency devices may just allow the natural process of healing to occur.

Long-term Results of Pectoralis Major Muscle Transposition for Infected Sternotomy Wounds

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During an 11.5-year period, 100 consecutive patients (79 male, 21 female) underwent repair of an infected sternotomy wound. Sixty-five patients had failed attempts at wound closure by other physicians. Median age was 61.5 years (range, 5 to 85 years). Reconstruction included muscle in 79 patients, omentum in 4, and both in 15. A total of 175 muscles were transposed, including 169 pectoralis major, 3 rectus abdominis, 2 external oblique, and 1 latissimus dorsi. Median number of operations was four (range, 1 to 11). Mechanical ventilation was required in 30 patients. Two perioperative deaths occurred, one related to sepsis. Median follow-up was 4.2 years (range, 1.3 to 13.5 years). Twenty-six patients had recurrent infection. Median time from our closure to recurrence was 5.5 months (range, 0.3 to 27.6 months). Cause of recurrence was inadequate removal of cartilage in 16 patients, bone in 6, and retained foreign body in 4. Eighteen patients had the wound reopened with further resection; 10 had another muscle or omentum transposition. There were 30 late deaths, only one related to recurrent infection. At the time of death or last follow-up, 92 patients had a healed chest wall. Transposition of the pectoralis major muscle remains an excellent method of management for infected sternotomy wounds. Failure is directly related to persistent infection of cartilage, bone, or retained foreign bodies.

MEDIAN STERNOTOMY IS the preferred approach for most cardiac operations and for resection of many anterior mediastinal masses.[1] Although wound complications after sternotomy are rare, infection remains the most threatening because of the potential for mediastinal sepsis with extension to aortocoronary grafts, cardiotomy incisions, and intracardiac prostheses.[2] In the past, the consequences of such infections have been death or a prolonged convalescence.[3-6] In 1980 Jurkiewicz and associates[7] revolutionized management of this complication by reporting excellent results in patients treated by vigorous sternal debridement and obliteration of dead space with healthy, viable muscle. In 1984 we reported[8] similar excellent results; however our follow-up was short-term. The purpose of this report is to review our long-term experience with recalcitrant infected sternotomy wounds that were managed primarily with muscle transposition and to analyze factors affecting long-term successful closure.

Patients and Methods

Between June 1, 1977 and November 21, 1988, 100 consecutive patients with infected median sternotomy wounds were treated at the Mayo Clinic by the combined efforts of a single thoracic and plastic surgeon (PC Pairolero, PG Arnold). This combined approach, however, does not represent the entire experience with such wounds at our institution during that time. Seventy-nine patients were male and 21 were female. Ages ranged from 5 to 85 years (median, 61.5 years). Sternotomy was performed for cardiac disease in 92 patients and for mediastinal disease in eight (Table 1). Seventy-four patients had coronary artery bypass; the internal mammary artery was used in 36 patients (left in 32 and both in 4). Ninety patients had a single previous sternotomy; 10 had multiple sternotomies, all for cardiac disease. Six patients had 2 cardiac operations, two had 3, and two had 4. Ten of the 100 patients had their sternotomy wound reopened during the immediate postoperative period because of bleeding or dehiscence; two other patients had emergent vagotomy and antrectomy for bleeding duodenal ulcers. Eight patients had received previous mediastinal irradiation for previous malignant disease. Forty-four patients had their sternotomies performed at another institution.

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TABLE 1. *Indications for Median Sternotomy*

Indication	Number of Patients	Previous Mediastinal Radiation (No. of Patients)
Cardiac	92	3
CABG	70	
CABG + AVR	2	
CABG + MVR	2	
MVR	4	
AVR	6	
MVR + AVR	3	
Fontan procedure	3	
Tetralogy of Fallot	2	
Mediastinal	8	
Cancer	5	5
Pneumothorax	2	
Aortoinnominate bypass	1	
Total	100	8

CABG, coronary artery bypass graft; AVR, aortic valve replacement; MVR, mitral valve replacement.

Sternal drainage occurred 1 week to 4 years after sternotomy (median, 3 weeks). The median time interval between the onset of sternal drainage and sternal repair by us was 7.5 weeks (range, 2 days to 6 years). During this latter time period, 65 patients had previous attempts at wound closure by other physicians that failed, which included debridement in all patients, mediastinal irrigation and suction drainage in 41, omental transposition in 2, and muscle transposition in 1. The median number of sternal debridements in these 65 patients before evaluation by us was two (range, 1 to 10). All patients had purulent sternal drainage.

Our initial treatment included debridement of the manubrium and sternum in all patients. Early in our experience mediastinal debridement was limited. However now we think that mediastinal debridement should be done in all patients, and great effort was made in our later experience to remove all exposed foreign bodies, including felt pledgets, pacemaker wires, and sutures.[9] If heart or great vessel suture lines required reinforcement because of real or potential bleeding, fascia lata and transposed muscle were used. In addition to debridement, the manubrium and sternum were resected completely in 43 patients and partially in 33; all 76 had associated costochondral arches resected from the back to the ribs.

Tissue cultures, obtained in all patients, were positive in 95. One hundred eighty-two organisms were isolated (Table 2). A single organism was identified in 45 patients, two in 24, three in 20, four in 3, six in 1, and eight in 1. Eighty patients had only bacteria identified, two had only fungus, and 13 had both. No patient had multiple fungi isolated.

Muscle or omental flaps were used to obliterate the underlying mediastinal space in 98 patients. In the remaining two patients, the skin wound was left to heal secondarily after debridement only. Reconstruction was entirely with muscle transposition in 79 patients, omental transposition in 4, and both in 15. Transposition of the various muscles and omentum has been described previously.[8,10–16] A total of 175 muscles were transposed, including 169 pectoralis major (all based on the thoracoacromial leash), 3 rectus abdominis, 2 external oblique, and 1 latissimus dorsi. Seven patients had myocutaneous flaps (rectus abdominis in 2, pectoralis major in 2, external oblique in 2, and latissimus dorsi in 1). Bilateral pectoralis major muscle transpositions were performed in 79 patients. The nondominant humeral attachment of the pectoralis muscle was divided in 114 of the 169 transpositions (65.7%).

The median number of operations in these 100 patients was four (range, 1 to 11). The wound was closed at the time of the initial debridement in 11 patients. In the remaining 89 patients, the wound was dressed with moist gauze after initial debridement and/or resection and four times a day thereafter. All wounds were thoroughly irrigated with water at the time of each dressing change. Additional debridements to remove nonviable tissue were done as needed. Quantitative tissue cultures were not obtained to determine the timing of wound closure. Instead the wound was closed when healthy granulation tissue was present without gross exudate. Wound closure was performed a median of 14 days after the initial debridement (range, 2 to 192 days) in 88 patients.

Hospitalization ranged from 7 to 210 days with a median of 26.5 days. Fifty-nine complications occurred in 42 patients (Table 3). Eight patients had prolonged wound

TABLE 2. *Micro-organisms Identified in 95 Patients with Infected Sternotomy Wounds*

Micro-organisms	Number of Patients
Bacteria	
Staphylococcus aureus	65
Pseudomonas aeruginosa	19
Streptococcus viridins	16
Staphylococcus epidermidis	13
Enterobactor	10
Serratia marcescens	8
Staphylococcus pyogenes	7
Escherichia coli	6
Cornybacteria	6
Propionibacteria	5
Hemophylis influenza	3
Klebsiella pneumoniae	3
Proteus vulgaris	3
Actinobacillus	1
Salmonella	1
Fungus	
Candida albicans	13
Rhizopus arrhizus	1
Aspergillus fumigatus	1
Trichoderma	1

TABLE 3. *Complications*

Complication	Number
Wound infection	8
Wound hematoma	6
Myocardial infarct	4
Muscle necrosis	2
Omental necrosis	2
Renal failure	2
Acute femoral artery occlusion	1
Mycotic popliteal artery aneurysm	1
T_{4-5} disc space infection	1
Wrist space infection	1
Subphrenic abscess	1

infections (5 superficial, 3 deep); 7 were dismissed with a portion of the wound healing secondarily, and 1 was open at the time of perioperative death. All 6 patients with wound hematomas required operative evacuation. All patients with distant sites of infection (popliteal artery, T_{4-5} disc space, wrist space, and subphrenic space) also required surgical intervention.

After each operative procedure, the patients generally were extubated on the evening of the operation. Mechanical ventilation beyond the second postoperative day, however, was required in 30 patients, 21 because of chest wall instability and 9 because of continuing sepsis. Two of the 21 patients with chest wall instability had tracheostomy; 1 was performed at another institution for unknown reasons, and 1 was performed by us for aspiration pneumonia. All wounds in these 21 patients were successfully closed, and extubation was possible in all by 14 days (median, 3.5 days). Six of the nine patients with sepsis had tracheostomy. Five of the wounds in these nine patients were closed and, again, extubation was possible in each. Extubation also was possible in one of the four patients in whom the wound could not be closed. The median length of mechanical ventilation in the five patients who were extubated was 45 days (range, 32 to 100 days).

Two perioperative deaths occurred. The first was in an 85-year-old man who underwent aortic valve replacement. Three weeks later the wound became infected. The patient had an uneventful course following debridement and closure with bilateral pectoralis major flaps until sudden death from a myocardial infarction 17 days later. The second death occurred in a 71-year-old man who had coronary artery bypass and who underwent emergency vagotomy and pyloroplasty on the 11th postoperative day for a bleeding duodenal ulcer. Bleeding continued and 4 days later he underwent antrectomy. This was followed by generalized sepsis, including mediastinitis and peritonitis. Although the mediastinum was debrided and bilateral pectoralis major flaps were transposed, the wound was never closed because of progressive respiratory and renal failure. Death occurred at 171 days.

One patient was lost to follow-up. This was a 61-year-old man who developed an infected sternotomy wound after coronary artery bypass. Although closed with bilateral pectoralis major flaps, sepsis continued and resulted in wound breakdown, respiratory failure, and tracheostomy. His hospital course also was complicated by acute common femoral artery occlusion that necessitated thrombectomy. However gradual improvement occurred and eventually he was transferred to his home hospital in Spain on the 88th postoperative day with both a tracheostomy and his sternum healing secondarily. Follow-up in the remaining 97 operative surviving patients ranged from 1.3 to 13.5 years (median, 4.2 years).

Seven patients were dismissed from the hospital with a portion of the sternal wound open. One patient was lost to follow-up and one died from sepsis at 3 months. The wounds in four of the patients healed spontaneously between 3 to 6 months, and one was closed with omentum and skin graft at 2 months.

Recurrent sternal infection occurred in 26 patients and was more frequent in the last half of our study period (in 21 of 66 patients) than in the first half (5 of 34 patients) ($\chi^2 = 2.584$, $p = 0.108$). Median time from our closure to recurrence was 5.5 months and ranged from 0.3 to 27.6 months. All recurrences presented as draining sinuses, most commonly associated with osteomyelitis and/or costochondritis. None had abscess collection in the mediastinum, pleura, or peritoneum, although several patients had draining sinus tracts to retained mediastinal foreign bodies. Drainage, erythema, and local tenderness were the most common findings. Other signs and symptoms were uncommon.

Factors possibly affecting recurrent sternal infection are shown in Table 4. Only inadequate removal of nonviable tissue at the time of definitive repair was significant. Those patients who had resection of the manubrium, sternum, and costochondral arches were significantly less likely to develop late recurrence (10 of 64 patients) than those who had debridement only (14 of 26 patients) ($p < 0.001$). The number of operations to close a wound successfully, the extent of resection (complete *versus* partial), a history of previous sternal irradiation, the number of previous sternotomies, the institution where the sternotomy was performed, the indication for sternotomy, and whether the internal mammary artery was used for cardiac revascularization did not affect recurrence (p = NS). Recurrence in our patients was attributed to inadequate removal of cartilage in 16 patients, bone in 6, and retained foreign bodies in 4.

Anterior chest wall pain was present in 37 patients. This pain was described as a stabbing sensation in 27 patients, tightness in 4, ache in 3, numbness in 1, and spasms in 1. The pain generally was always present, made worse by activity, and usually not relieved by analgesics or other pain clinic techniques. Symptoms were more common in

TABLE 4. *Factors Affecting Long-term Successful Closure*

Factors	Recurrence	No Recurrence	p Value*
Removal of tissue			
Debridement	14	10	
Resection	12	64	0.001
No. of operations			
Single	0	11	
Multiple	26	63	0.086
Extent of resection			
Complete	7	36	
Partial	5	28	0.854
Sternal radiation			
Yes	2	6	
No	24	68	0.724
No. of prior sternotomies			
Single	25	65	
Multiple	1	9	0.403
Institution			
Mayo Clinic	14	42	
Other	12	32	0.978
Indication for sternotomy			
Cardiac	23	67	
Mediastinum	3	7	0.939
Coronary artery bypass			
Mammary artery	8	28	
Vein only	14	24	0.262

* Chi square test.

patients who developed recurrent infection (19 of 26 patients) than in those who did not (18 of 74 patients) ($\chi^2 = 17.582$, $p < 0.001$). Five of nineteen patients with omental transpositions developed hernias through the tunnel through which the omentum was passed. All five patients were asymptomatic and none required surgical intervention. Progressive shortness of breath during follow-up was uncommon.

The wound healed spontaneously in 7 of the 26 patients with recurrent infection. One patient refused further surgical treatment and the wound currently continues to drain. The remaining 18 patients underwent additional operative procedures. All patients had further removal of nonviable tissue, 10 by debridement of residual manubrium, sternum, and cartilage, and eight by resection. Eight of these patients had debridement or resection only, seven also had another muscle transposition, and three had omental transposition. Retained foreign bodies also were removed from four patients. Following these procedures 13 patients had no further signs or symptoms of infection; however infection recurred for a second time in five patients, all of whom had had debridement rather than resection as management for the first recurrence. Three of these five patients underwent additional resection and a third muscle transposition, one had debridement only, and one refused further surgical intervention. At last follow-up the wounds in three of these five patients were healed, and two continue to drain (one patient who had debridement and one who had resection). In summary 22 of the 26 patients with recurrent sternotomy infections now have well-healed chest wounds without drainage.

There were 30 late deaths, only one related to infection. This patient was a 71-year-old man who had an uneventful course after wound closure with bilateral pectoralis major flaps. Although discharged from the hospital, infection persisted in this man. The wound was reopened and debrided, but adult respiratory distress syndrome developed and the patient died 2.5 months after initial closure. Cause of the death in the remaining 29 patients was cardiac in 20, cancer in 3, renal failure in 1, trauma in 1, radiation myelitis in 1, and unknown causes in 3. At the time of death, 27 patients had healed chest walls.

There were 98 operative survivors; one was lost to follow-up and one died after 2.5 months from continuing infection. Twenty-six patients developed recurrent sternal infection, 22 of whom were successfully treated. Sixty-seven patients are known to be alive. Median follow-up in these 67 patients was 4.7 years (range, 0.7 to 13.5 years). Sixty-five of these former patients have healed anterior chest walls. At the time of death or last follow-up, 92 patients had healed chest walls without drainage.

Discussion

Since 1957 median sternotomy has become the most commonly used incision in cardiac operations.[17] The rapidity and ease with which it can be performed and the excellent access it provides to the heart and great vessels are major factors contributing to its widespread acceptance. Although wound complications are few, infection remains the most ominous.[18,19] If left untreated these infections can extend to aortic and cardiac suture lines, prosthetic grafts, and intracardiac prostheses and can result in death.

The earliest treatment of infected sternotomy wounds consisted of debridement and open sternal drainage, which had an attendant mortality rate of more than 50%.[20] Shumacker and Mandelbaum[3] and Bryant et al.[4] subsequently described the technique of closed mediastinal irrigation and suction drainage, which reduced the mortality rate to approximately 20%. In 1976 Lee, et al.,[21] offered an alternative method of management by transposing the omentum to eliminate mediastinal dead space. Jurkiewicz and associates expanded this concept by using pectoralis major muscle flaps and reduced the mortality rate to zero.[7] Since then these and other authors reported equally excellent results in large numbers of patients, often using multiple stages.[8,22–28]

Nearly all authors agree that the pectoralis major muscle is ideal to manage patients with complicated infected median sternotomy wounds. The muscle has a dominant blood supply based on the thoracoacromial artery. Mobilization of this muscle allows an arc of rotation that reaches all of the anterior chest wall except the lower sternum. Nonetheless treatment of infected sternotomy wounds continues to be controversial. Recently good results were reported with less extensive and single-stage procedures, suggesting that extensive debridement and multiple operations may not be necessary.[29,30] However most reports fail to distinguish between the different types of sternal wound infections and none report factors that influence successful long-term closure.

Clearly not all infected median sternotomy wounds require muscle or omental transposition. Superficial infections may be treated successfully by adequate drainage, specific parenterally administered antibiotics, local wound care, and simple secondary closure. Deeper infections that involve the sternum and the anterior mediastinum, however, require exploration and thorough debridement.

Deep infected median sternotomy wounds present in one of three ways (Table 5).[31] The earliest are type I infections. These patients present with serosanguineous wound drainage within a few days of sternotomy. Few patients have skin cellulitis; none have mediastinal suppuration, osteomyelitis, or costochondritis. Wound cultures often demonstrate no growth; when positive, however, a staphylococcal species is encountered in nearly 50% of cases. Early recognition of type I wound infection requires a high index of suspicion and they are best managed in the operating room under general anesthesia, where both the subcutaneous and mediastinal spaces can be inspected. Because the mediastinum is always soft and pliable, residual space is obliterated easily by suction drainage, thereby allowing the wound eventually to heal in most patients. A few, however, will progress and will require more extensive debridement with obliteration of dead space by viable tissue. Our experience with type I wound infection is minimal because most are managed by the operating cardiac surgeon. Nonetheless 11 of our patients had this early type of infection; all were managed with a single operative procedure and none developed recurrent infection. Equally important is the fact that 41 of our patients had mediastinal irrigation and suction drainage with immediate closure by other surgeons, yet infection progressed in all. When we evaluated these 41 patients, all had type II infection, as described below, and all required more extensive operations. We could not determine historically what type of infection was present at the time of previous treatment at other institutions.

TABLE 5. *Classification of Infected Sternotomy Wounds*

Classification	Number of Patients
Type I	11
Occurs within first few days	
Serosanguineous drainage	
Cellulitis of skin absent	
Mediastinum soft and pliable	
Osteomyelitis and costochondritis absent	
Cultures usually negative	
Type II	84
Occurs within first few weeks	
Purulent drainage	
Cellulitis of skin present	
Mediastinal suppuration	
Osteomyelitis frequent, costochondritis rare	
Cultures positive	
Type III	5
Occurs months to years later	
Chronic draining sinus tract	
Cellulitis of skin localized	
Mediastinitis rare	
Osteomyelitis, costochondritis, or retained foreign body always present	
Cultures positive	
Total	100

Type II infections present as fulminant mediastinitis usually within the first few weeks after operation. These patients often have purulent wound drainage, skin cellulitis, and obvious communication between the sternum and mediastinum. Many have acute osteomyelitis but only a few have associated costochondritis. Cultures usually are positive for staphylococcal species. Like type I infections, our practice is to inspect type II wounds in the operating room under general anesthesia, where all recesses of the mediastinum must be explored thoroughly. Necrotic tissue such as bone, cartilage, or soft tissue should be excised. Any exposed healthy cartilage should be resected back to normal bone.[32] The cut surface of cartilage is at greater risk of recurrent infection than the cut surface of bone. All foreign material, including sutures, pledgets, and sternal wire, are removed. Every effort should be made to avoid entering the pleural space if there is no clinical or roentgenographic evidence of empyema.

The key to deciding whether type II wounds can be closed at the time of initial debridement is the condition of the mediastinum. If soft and pliable, suction drainage usually will obliterate mediastinal space after the sternum is closed following debridement. Obliteration of dead space below the sternum combined with muscle transposition on the external surface usually will prevent reinfection and many wounds will heal with this technique. However there is a group of patients with advanced type II infections in which the suppuration has caused the mediastinum to become indurated and thickened. As a result pliability decreases and mediastinal dead space cannot be obliterated by suction drainage alone. These wounds mandate obliteration of this space by other techniques. Late type II infections were the most common wound we treated. It was also the wound most likely to develop recurrent infection. These latter findings probably reflect the tertiary nature of our practice and explain why recurrent infection was more common in the last half of our experience (31.8%) than in the first half (14.7%), although this difference is not statistically significant.

Type II wounds that are not closed immediately are dressed with gauze moistened with saline solution following thorough resection. The dressing is changed in the patient's room every 4 to 6 hours and the wound irrigated with water. If possible the patient showers because drainage is considerably better in the upright position. If bedridden irrigation is done in a special treatment facility with a hand-held shower or Water Pik (Teledyne, Inc., Fort Collins, CO).[33] If at any time there is evidence of new or persistent necrotic tissue, the patient is returned to the operating room for further debridement.

Closure of the wound is performed when there is no evidence of drainage, when nonviable periosteum, perichondrium, bone, or cartilage has all been removed, and when the edges of the debrided sternum or ribs are clean. Our first choice to obliterate the mediastinal space is the pectoralis major muscle transposed on the dominant proximal thoracoacromial neurovascular leash. Frequently both pectoralis major muscles are mobilized. The nondominant humeral attachment is divided as needed to permit the degree of rotation and advancement required; sometimes both humeral attachments must be divided to close the wound. The overlying skin and subcutaneous tissue then are closed with direct suture. We also prefer to close the lower portion of the wound with skin and subcutaneous tissue rather than the rectus abdominis muscle because recurrences, in our experience, were not related to this portion of the wound. Myocutaneous flaps are used on rare occasions when they seem to be the best geometric solution to a wound of a particular size, shape, and location. If the epicardium is exposed, the omentum may be transposed to obliterate any pericardial space and to cover the heart, if necessary. The more superficial layers of the chest wall then are closed by skin graft, muscle flaps, or direct closure of skin and subcutaneous tissues.

Sometimes the pectoralis major muscles are absent or insufficient to close the wound. In these patients consideration must be given to other types of transposition; we prefer omental or rectus abdominis muscle transposition. Both of these flaps should be considered second-line treatment choices. Omental transposition has the distinct disadvantage of both entering a sterile visceral cavity and producing a ventral hernia. One of our 19 patients who had omental transposition developed a subphrenic abscess because of this procedure and five developed hernias. The rectus abdominis muscle flap may not be as dependable if the internal mammary artery has been used in a coronary artery bypass, thrombosed from infection, or ligated with sternal debridement.

Type III infections occur months to years later. These patients present with a chronic draining sinus tract from the manubrium, sternum, costochondral arches, or retained foreign bodies. All have osteomyelitis and/or costochondritis but mediastinitis is rare. Most patients also have localized skin cellulitis around the sinus tract site. Cultures often are positive. When the sinus tract is explored, all infected bone and necrotic tissue must be resected back to healthy bone. If the sinus tract extends into the mediastinum, usually there is retained foreign material and this also must be removed. If the sinus tract enters cartilage, the entire cartilage must be resected back to normal bone. After debridement we prefer to dress this wound open with frequent dressing changes and repeat debridement as indicated. Once the wound is clean, closure is as described above with preference given again to pectoralis major muscle transposition.

Twenty-six per cent of our patients developed recurrent infection. Interestingly the recurrence rate was nearly identical for both the second (28%) and third (25%) surgical attempts to heal the wounds. When factors affecting recurrent infection were analyzed, only incomplete removal of nonviable tissue was significant. Those patients who had debridement only had a significantly greater chance of developing late recurrence as compared to those who had resection; this observation also was true after the second and third attempts at surgical wound healing. Although not statistically significant, no recurrence occurred in patients in whom we were able to close the wound in one procedure. We think, however, that this is so only because of the small number of patients involved.

Recurrent infections often were managed with another muscle transposition in addition to debridement or resection. Most transpositions involved the same pectoralis major muscle in that the previously transposed muscle was remobilized to allow debridement or resection and then retransposed. None of our patients had loss of muscle with this technique.

Long-term respiratory failure after successful wound healing was unlikely and was not related to whether mechanical ventilation was required during the time of sternal wound management. Instead progressive shortness of breath was related more commonly to late cardiac failure. This observation correlates with our previous experience with resection of the anterior chest wall for neoplasms.[34]

We conclude that there is a spectrum of infected sternotomy wounds and that all follow the same time-honored principles of wound healing elsewhere: the wound must be drained adequately; all necrotic tissue, devascularized tissue, and foreign material must be removed; and all residual space must be obliterated. If these principles are achieved, the entire spectrum of sternotomy wound infections can be healed successfully. For patients with late, recalcitrant median sternotomy wound infections, these principles are best achieved by sternal resection combined with pectoralis major muscle transposition.

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DISCUSSIONS

DR. FRANCIS ROBICSEK (Charlotte, North Carolina): I agree with Dr. Arnold and his coworkers that the pectoralis muscle is perhaps the surgeon's best friend, and in our practice we use it not only to treat sternum infection but also to prevent some of the complications before they occur.

We use it in especially two types of patients. In very thin women who are liable to develop sternal complication, we mobilize the pectoralis muscle back to about 1.5 or 2 inches, more on the side where the mammary is intact and unite it in the front of the sternum. This gives an excellent soft padding. And in our experience, the wound healing is much better.

The second type of patients in whom we use this method are heavyset, robust individuals, especially those with obstructive pulmonary-arterial disease.

I believe that the pectoralis muscle, besides being a friend, is also a culprit that causes or contributes to some of the disruptions by pulling the sternum apart. If you reverse this process by uniting it in the front of the sternum, then the pectoralis muscle is working for you instead of against you.

We also use this method in sternal disruptions, even before the infection occurs. In such cases we do the sternal weaving around the wire down on the sides of the sternum then unite the pectoral muscle in the front of the sternum. In practically all of the cases, you can obtain a very nice healing.

Use of muscle flaps in thoracic infection is probably the most important development in the history of thoracic surgery in the last decade. And for this Dr. Arnold and his colleagues who have pioneered this procedure deserve the gratitude of the profession.

DR. M. J. JURKIEWICZ (Atlanta, Georgia): A 2% perioperative mortality rate for patients such as Dr. Arnold shows is outstanding.

These are our data from Emory University in roughly the same time period. I am uncertain, really, whether our patient population is similar because they have had a patient cohort, 44% of whom had their sternotomies performed elsewhere.

Most of our patients are generated within the University. We have about a 10% rate of patient referral from other institutions for this problem. As you can see, during that time period we had 246 patients with infection, for an infection rate of about 1.6%, which is roughly that which is average for the field. Of those 35 were superficial and easily treated, and 211 had mediastinitis.

These are the flaps we used. We used pectoralis, but we have turned in recent years to the use of the rectus abdominus. We used roughly in 139 patients a single-stage closure and a two-stage closure such as they use at the Mayo Clinic in 38% of the patients.

Our duration of hospitalization was 15.7 days after treatment.

The perioperative mortality rate we had with these patients was 5.3%. Our persistent drainage rate was 0.8%. That figure really should be merged with all of these others here because we had roughly the same recurrence rate that Dr. Arnold has had and for the same reasons, inadequate debridement. We have turned to single muscle for closure in recent years, and this reflects experience with the rectus abdominus muscle.

Now the treatment of medial sternotomy wound infection remains uncertain and by no means settled. Drs. Arnold and Pairolero have made a significant contribution, I believe, by devising appropriate classification of these wounds associated with frank mediastinal infection.

Another important observation is that the condition of the mediastinal viscera is of help in sorting out those patients who need muscle flaps.

Early diagnosis clearly is the key. The data from New York University reported by Grosse and Frank Spencer were stratified into those patients treated before and after 20 days following their sternotomy. Those patients treated before 20 days did much better than those patients treated after 20 days.

Drs. Arnold and Pairolero, in their type 2 patients, used pliability of the mediastinum as a guide. When pliable, the closure over suction drainage is successful. Otherwise they advocate muscle flaps, as Frank Spencer has come to advocate in late cases.

It is not clear to me, Peter, whether you used closed catheter irrigation plus systemic antibiotics in these patients. I would ask you to comment on that in your closing.

DR. BOBBY HEATH (Jackson, Mississippi): Certainly, as cardiac surgeons, we consider this one of our more dreaded complications. And as you know from the literature, it is from 0.1% to 2.5% as a complication rate.

Because of such horrible results with the tube drainage and irrigation systems that we experienced during my residency, our initial patients were treated by a very early and radical debridement from skin, subcutaneous tissue, sternum, and even mediastinal contents to include the pericardium, then transferred the omentum into the mediastinum and closed the sternum primarily along with the sternal fascia and the skin.

We reported on eight of these patients, seven of whom survived, and all their incisions healed, and none have recurred in a 1- to 9-year observation period.

I would certainly echo what Dr. Arnold said about the absolute and complete debridement of all the infected areas and foreign material. Also the time that the diagnosis is made of the acute infection is very important.

Sometimes it is difficult to make the diagnosis because of the lack of systemic symptoms. There may be only a slight increase in the sternal pain and, otherwise, the drainage and the unstable sternum may be the only other findings.

It is very important that we have very early recognition of this potential problem, very early institution of broad-spectrum antibiotics, then to be specific when an organism is known. And this is to be followed emergently by radical debridement and whatever treatment choice you might propose. This is more important than transferring the omentum or the tube drainage system, as is advocated by many.

The omentum in the mediastinal dead space may be important in the reduction of recurrences, as has been seen in Dr. Arnold's chronic problems.

DR. PETER PAIROLERO (Closing discussion): Dr. Robicsek, we agree with you completely that the most exciting thing that has happened in general thoracic surgery in the last decade has been the development of muscle flaps. These have greatly improved management of those patients who have had various types of thoracic infection.

From the standpoint of prophylactic repair at the time of initial sternal closure, your concept certainly makes sense. The fact that turnover pectoralis muscle flaps may compress the sternotomy wound could potentially lead to increased bone healing.

We would like to stress that there is a spectrum of infected sternotomy wounds. Type 1 wounds occur within days after operation; type 2 within weeks; and type 3, months to years later. All type 3 wounds present as osteomyelitis and costochondritis.

Most of our patients had type 2 wounds. The diagnosis of type 1 infection is difficult to make. Cellulitis is often absent, cultures are frequently negative, and mediastinitis is always absent. All have a soft, pliable mediastinum that can be obliterated by suction drainage when the wound is closed, allowing the wound to heal.

In contrast type 2 wounds have cellulitis and purulent drainage. All, as Dr. Arnold has demonstrated, have mediastinitis resulting in a stiff mediastinum, which often cannot be obliterated with suction drainage. Consequently drainage alone frequently is inadequate, and we do not use suction drainage, Dr. Jurkiewicz, for patients with type 2 infection. All, however, are receiving parenteral antibiotics. Type 3 wounds require debridement of all infected cartilage, bone, and retained foreign bodies.

Dr. Jurkiewicz 56 of our patients were from our practice and 44 came from elsewhere. Where the patient was referred from did not make any difference insofar as recurrence was concerned.

We debride most patients because of the advanced nature of the infection (type 2). Invariably the internal mammary artery is ligated if it has not been used as a conduit for the coronary artery bypass. Consequently we do not use the turnover pectoralis major muscle or the rectus abdominis muscle. Our practice has been to use the omentum as a backup procedure.

The condition of the wound, *i.e.*, clean without exudate, is the major determinant of when it should be closed. Based on our results, the pectoralis major muscle transposed on the thoracoacromial vessel is a very good choice for management of recalcitrant median sternotomy wounds.

Identification, Characterization, and Quantitation of Soluble HLA Antigens in the Circulation and Peritoneal Dialysate of Renal Patients

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Human lymphocyte antigen (HLA) class I and class II antigens and beta$_2$ microglobulin (B$_2$M) were identified in peritoneal dialysate (PD) and serum from patients with end-stage renal disease (ESRD) using monoclonal antibodies in an enzyme-linked immunoassay. The HLA class I and class II antigens each exhibited approximate molecular weights of 50,000 to 60,000 daltons by chromatography on Sepharose CL 6B. Class I antigens in serum and PD fluid were associated with B$_2$M. Free B$_2$M (Mr 11,500) also was detected in both sera and PD fluids. Unlike class I antigens, class II antigens were not found to have attached B$_2$M. Class I and class II antigens eluted from 2-diethylaminoethanol ion exchange gradient columns at 0.07 mol/L (molar) phosphate buffer pH 7.2 and migrated with alpha$_2$ -beta$_1$ mobility in agarose electrophoresis. Class I antigens were purified from ESRD patients' PD fluid by solid-phase immunoaffinity chromatography. Enzyme-linked immunoassay demonstrated that this purified protein was composed of a class I heavy chain and B$_2$M. Class I allospecificity was confirmed by neutralization on known HLA typing antisera in a microcytotoxicity assay. Soluble HLA class I antigen preparations specifically inhibited blast transformation of responder lymphocytes in mixed lymphocyte culture reactions. Inhibition was dose dependent and ranged from 0% to 95%. The presence of soluble HLA antigens in body fluids may play an important part in the immunologic tolerance to self. This study demonstrates a ready source of large quantities of soluble HLA for detailed analysis.

CLASS I PRODUCTS of the major histocompatibility complex (MHC) are composed of a glycosylated and highly polymorphic heavy chain of 40 to 50 kd encoded by class I genes of chromosome 6 and are associated noncovalently with an unglycosylated B$_2$M light chain of approximately 11 kd. The beta$_2$ microglobulin (B$_2$M) light chain is necessary for incorporation of class I glycoproteins into the plasma membrane.[1] Each heavy chain has 5 protein domains: 3 extracellularly, 1 transmembrane, and 1 cytoplasmically.[2] Most human lymphocyte antigen (HLA) is attached to cell membranes, although it has been known since 1970 that trace amounts of soluble HLA in serum could be demonstrated by indirect methods.[3] Technical advances have now made it possible to study soluble HLA in more detail using direct measurements. Monoclonal antibodies directed against the constant region of all class I MHC antigens are now available.[4] The use of these monoclonal antibodies along with others directed against alloantigen domains made it possible to demonstrate that at least some recipients of liver transplants secreted HLA in soluble form of the donor phenotype.[5] Some observations suggest that such soluble compatibility antigens may play a major role in the maintenance of self tolerance[6] and, thus, might be useful in the induction of tolerance.[7,8] Therefore the careful study of this soluble fraction of HLA is potentially important, and a source of large quantities of such antigen would facilitate those studies.

We developed a solid-phase enzyme-linked immunoassay for (ELISA) quantitating soluble HLA, regardless of phenotype, in serum and other body fluids and have characterized the class I antigen found in patient sera and peritoneal dialysate (PD) fluid.

Methods

Sample Collection

Sera were obtained from normal adult volunteer blood donors and transplant and end-stage renal disease (ESRD) patients. Peritoneal dialysates were obtained from ESRD patients undergoing therapeutic peritoneal dialysis. Sera

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from all individuals were separated from the clot within 3 hours of collection. Dialysate fluid was collected and concentrated approximately 25 times using a hollow fiber ultrafiltration unit immediately after dialysis. All samples were maintained at −20°C until analyzed.

Preparation of Monoclonal Antibody

Hybridoma cell lines AB 2.06 (anti-HLA DR monomorphic), W6/32 (anti-HLA A, B, C), and L368 (anti-human B_2M) were obtained from American Type Culture Collection (Rockville, MD). Cell lines were placed into culture, expanded, and monoclonal antibodies were produced in BALB/C mice. Monoclonal antibodies were isolated from ascites fluids using a goat anti-mouse immunoglobulin G (IgG) column. Affinity-purified monoclonal antibodies were concentrated to 1 mg/mL. Purity was confirmed by electrophoresis in agarose.

Column Chromatography

Size chromatography was performed on a Sepharose CL 6B column (1.5 × 100 cm) equilibrated in and eluted with TRIS saline (0.05 mol/L [molar] TRIS, 150 mmol/L [millimolar] NaCl, pH 7.3). Five milliliters of sample were applied to the column and eluted at a constant flow rate of 12 mL/hour by peristolic pumping. Four-milliliter fractions were collected. The elution profile at 280 nm was monitored constantly with an ISCO UA-4 absorbance monitor (ISCO Instruments, Lincoln, NE). Class I antigen and B_2M were measured by ELISA. Class 2 antigen was measured by dot-blot immunoassay.

Ion exchange chromatography was carried out using 2-diethylaminoethanol (DEAE) cellulose packed into a glass column (1.5 × 10 cm) and equilibrated with phosphate buffer 0.01 mol/L pH 7.3. A 15-mL sample containing the class I and class II antigens obtained from Sepharose CL-6B chromatography was loaded and the column was washed with equilibration buffer. Classes I and II antigens were eluted with a linear phosphate gradient (0.01 to 0.2 mol/L).

HLA–Beta$_2$ Microglobulin Association

The association of HLA class I and class II antigens with B_2M was evaluated by solid-phase ELISA. For the capture of class I and class II antigens, two sets of polystyrene beads (6.5 mm) were coated with purified monoclonal anti-HLA class I (W6/32) and purified monoclonal anti-class II (Ab2.06), respectively, as described below. In addition both monoclonal antibodies (W6/32 and Ab2.06) were conjugated with horseradish peroxidase by the method of Nakani.[9] B_2M was captured and detected with reagents obtained from INCSTAR. Under assay conditions, 200 μL of the 50,000-dalton and 11,000-dalton fractions from Sepharose CL 6B chromatography and bovine serum albumin (BSA) were added to their respective wells. Antibody-coated beads (anti-class I, class II, and B_2M) then were added to their respective wells and the reaction was incubated at 37°C for 1 hour. The beads were washed three times with distilled water and 200 μL of the appropriate peroxidase-labeled monoclonal antibody was added. The reaction was incubated for 1 additional hour at 37°C. The beads then were washed three times with distilled water and peroxidase activity was measured using 300 μL of O-phenylenediamine substrate. The enzyme reaction was carried out for 30 minutes at room temperature, terminated with H_2SO_4 (IN), and absorbances were measured at 492 nm. Intensity of color was proportional to the concentration of the antigen under study.

HLA A,B,C Purification by Immunoaffinity Chromatography

Monoclonal antibody W6/32 was coupled covalently with cyanogen bromide-activated Sepharose CL-4B.[10] Peritoneal dialysis fluid (25 L concentrated to 500 mL) from four individual patients was chromatographed on the anti-HLA A,B,C-Sepharose (2 × 10 cm) column at a flow rate of 100 mL/hour. The unbound proteins were removed by extensively washing the column with phosphate-buffered saline (PBS, 150 mmol/L NaCl, 20 mmol/L phosphate buffer, pH 7.3). Antibody-bound HLA was eluted with glycine HCl buffer (0.1 mol/L glycine, pH 2.5). Fractions were neutralized immediately with 1 mol/L dibasic sodium phosphate and dialyzed against PBS.

Dot-blot Immunoassay

Protein samples were dot blotted onto cellulose nitrate membranes using the procedure of Hawkes et al.[11] Membranes were blocked with 3% gelatin in TRIS-buffered saline (20 mmol/L TRIS; 500 mmol/L NaCl, pH 7.5), followed by overnight incubation with monoclonal anti-HLA (W6/32). The membranes were washed thoroughly with TRIS-buffered saline, pH 7.5, containing 0.05% Tween 20, followed by incubation with peroxidase-labeled goat anti-mouse IgG for 2 hours. The membranes were again washed, as described above, and the color reaction developed using 4-chloro-1-naphthol as the horseradish peroxidase substrate in TRIS-buffered saline, pH 7.5, with 0.01% H_2O_2.

Protein Determinations

Protein was quantitated using the protein assay kit BCA (bicinchoninic acid) from Pierce (Rockford, IL).

ELISA for Serum HLA A, B, and C Loci Antigens

Human lymphocyte A, B, and C locus antigens were quantitated in all patient samples by a solid-phase ELISA sandwich procedure.[12] Polystyrene beads (6.5 mm) were obtained from Precision Plastic Ball Co. (Chicago, IL) and coated with purified monoclonal anti-HLA (W6/32) at a concentration of 25 μg IgG per milliliter in PBS for 3 hours with shaking at 37°C. Beads were washed with PBS and incubated for 2 hours at 37°C with 10% BSA in PBS to block nonbound reactive sights and reduce nonspecific background reactivity. Antibody-coated, BSA-blocked beads were washed and stored in PBS containing sodium azide (1 mg/mL) at 4°C. Beads treated in this manner were very stable with less than 5% loss in antigen-binding reactivity during a 4-month period. New lots of beads were prepared as needed. With each assay six standards, a control serum, and patient sera were analyzed in duplicate. Under assay conditions, 200 μL of standard, control serum, and test serum were added to their respective wells. An antibody-coated bead was added to each well and the reaction was carried out at 45°C for 1 hour. The beads then were washed three times with distilled water. Two hundred microliters of peroxidase-labeled monoclonal anti-B_2M (INCSTAR Corp., Stillwater, MN) were added to each bead and incubated for an additional hour at 45°C. Beads were washed three times with distilled water; the color reaction for peroxidase activity was started by adding 300 μL of O-phenylenediamine substrate to each bead. The color reaction was terminated after 30 minutes by the addition of 1 mL of H_2SO_4 (1N) to each tube. Absorbance was measured at 492 nm. The peroxidase activity was proportional to the HLA class I antigen concentration.

ELISA for B_2M Quantitation

B_2M was quantitated by the MEIA procedure on the IMX System of Abbott Diagnostics (Abbott Diagnostics, Abbott Park, IL).

HLA Typing Trays and Neutralization Experiments

Human lymphocyte antigen tissue typing trays for class I and class II antigens were obtained from Terasaki and Gentrak. Neutralization experiments used either affinity-purified class I antigen or BSA as the control. Alloantibody containing tissue typing trays were loaded with either 1 μL of BSA or class I antigen. Trays were incubated for 1 hour at room temperature. Immediately after the incubation the soluble HLA donor was tissue typed using the class I antigen-neutralized tray and its corresponding BSA control tray. A standard complement-mediated cytotoxicity reaction then was performed. A reaction was scored as neutralized when a twofold (or greater) decrease in reactivity was observed.

MLC Inhibition Assay

A standard MLC reaction was performed with minor modification. Sixty microliters of both stimulator (mitomycin C killed) and responder cells containing 2 × 10^6 mononuclear cells in minimum essential medium (MEM) with 20% fetal bovine sera were pipetted into 96-well tissue culture plates. Thirty microliters of affinity-purified, saline-dialyzed, millipore filter sterilized, soluble class I antigen from the stimulator cell donor at varying concentrations is added to the appropriate microculture. Cultures were carried out for 4 days, at which time they were pulse labeled with tritiated thymidine. Cultures were harvested 24 hours later using an automatic cell harvester. Incorporated thymidine was counted by liquid scintillation. Changes in incorporated counts/minute were related to control counts per minute.

Results

Column Chromatography

HLA class I, class II, and B_2M initially were located by dot-blot immunoassay in column fractions obtained by the chromatography of concentrated PD fluid and sera from ESRD patients on a Sepharose CL 6B column. As shown in Figure 1, class I, class II, and B_2M eluted in tubes C-1 through C-4 with an approximate molecular weight of 50,000 to 60,000 daltons. In addition B_2M also

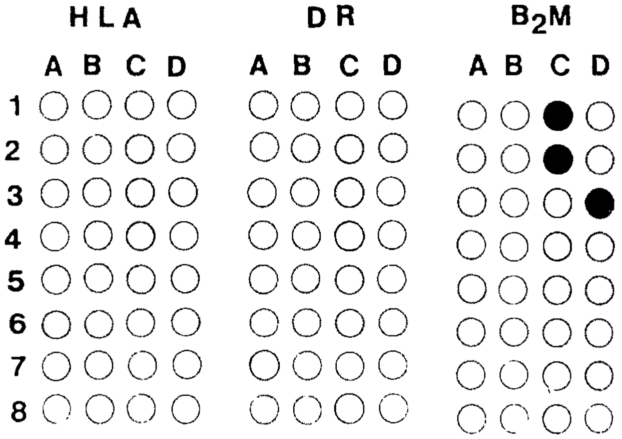

FIG. 1. Dot-blot immunoassay for HLA (Class I), Dr (Class II), and B_2M chromatographed on Sepharose CL 6B. Analysis of each antigen started on column fraction A1. Alternate tubes were analyzed. Weak reactivity to HLA class I was identified in tubes A1, A2, and A3. The principal HLA class I peak was identified in positions C1–C5. B_2M demonstrated two primary peaks: one corresponded to the position of HLA (C1–C5), while a second primary peak eluted in tubes D1–D7.

eluted later with peak reactivity in tube D-3 and continued through tube D-7 with an approximate molecular weight of 11,000 daltons.

More precise and quantitative measurements for class I antigen and B_2M subsequently were obtained by ELISA. As shown in Figure 2, class I antigen from ascites fluid was eluted within the albumin peak with an approximate molecular weight of 50,000 to 60,000 daltons. A minor class I peak also was identified at the void volume of this column (tubes 22 through 33). This may represent shed class I antigen in conjunction with cell membrane components. The primary HLA class I and B_2M eluted in tubes 60 to 70. B_2M also eluted in tubes 78 to 90 free of HLA.

The elution pattern for serum class I antigen and B_2M is shown in Figure 3. Minor differences between serum and PD chromatographs were observed. In serum the class I antigen peak at the void volume of the column was consistently absent (Fig. 3). A minor class I peak at approximately 110,000 daltons was consistently present (tubes 52 to 62) and may represent a dimer. The primary class I and B_2M peaks were essentially identical for these two columns (Figs. 2 and 3). These data indicate that HLA class I and B_2M cannot be separated by size.

DEAE Ion Exchange Chromatography

Column fractions from Sepharose CL-6B chromatography containing class I and class II antigens were subjected to chromatography on DEAE (Fig. 4). Class I antigen eluted with an approximate phosphate concentration of 0.07 to 0.08 mol/L. Dot-blot analysis for class II demonstrated that it eluted in essentially the same position (data not shown). These data indicate that HLA class I and B_2M cannot be separated by charge.

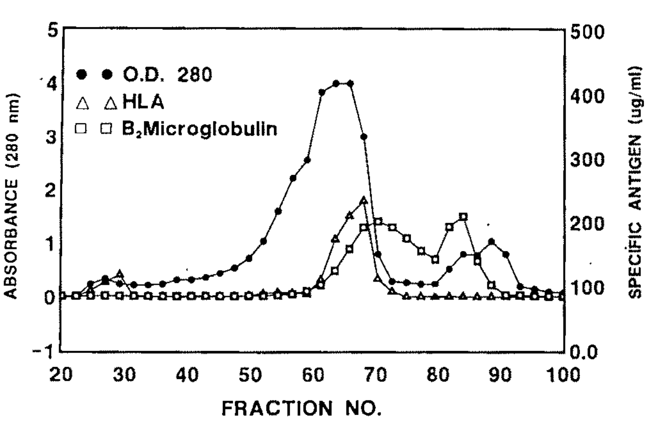

FIG. 2. Sepharose Cl 6B chromatography of PD concentrate. HLA primarily eluted in fractions 60–70. B_2M showed a biphasic elution pattern with the first peak corresponding positionally to that of HLA (molecular weight 50–60 kd). The second B_2M peak eluted in tubes 80–88 with an approximate molecular weight of 11 kd.

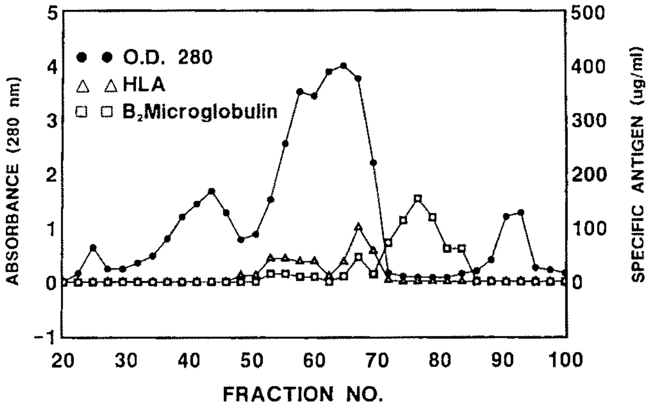

FIG. 3. Sepharose Cl 6B chromatography of serum. HLA principally eluted in fractions 60–70. A heavier species eluting in tubes 50–60 was identified and may represent a dimer. B_2M showed a biphasic elution pattern. The first peak corresponded positionally to that of HLA. The primary B_2M peak eluted between tubes 70 and 85 with an approximate molecular weight of 11 kd.

Immunoaffinity Purification of HLA Class I Antigen

HLA class I antigen was purified from six concentrated PD fluids from different patients by solid-phase affinity chromatography using monoclonal antibody W6/32 covalently attached to Sepharose CL-6B. A typical purification is shown in Figure 5. Most of the protein passes through this column unbound. Analysis of the nonbound fraction revealed that it was free of class I antigen. Class I antigen was eluted with glycine HCl buffer. Rapid neutralization of the glycine-HCl–released class I antigen was essential and typical recoveries ranged from 70% to 90%.

Solid-phase Cocapture Experiment for B_2M Association

To determine if B_2M was complexed with the class I and class II antigens eluting from the Sepharose CL 6B

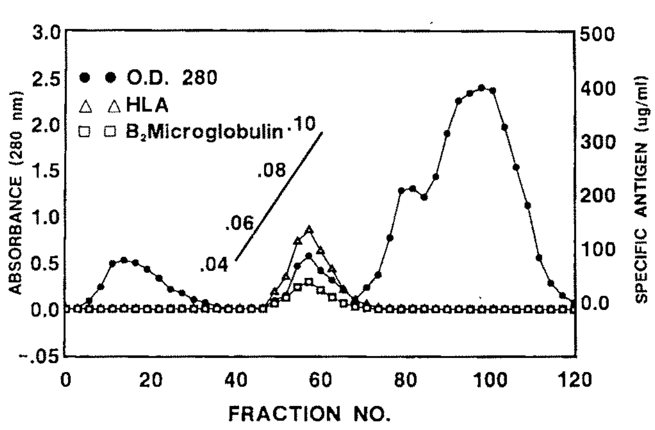

FIG. 4. DEAE fractionation of Sepharose CL 6B separated HLA. HLA and B_2M coeluted from DEAE with a phosphate gradient between 0.07 and 0.08 mol/L (molar). Neither HLA nor B_2M were detected in other fractions.

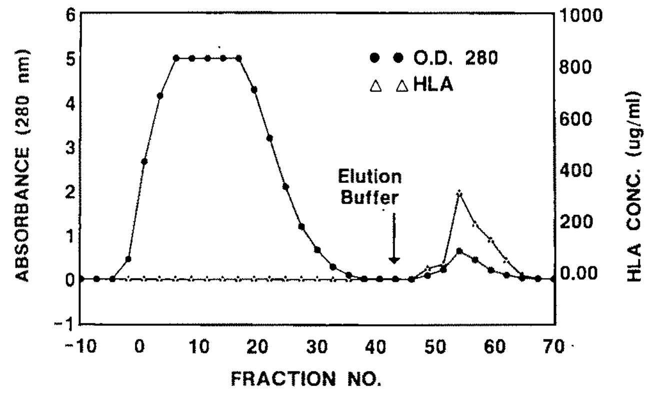

FIG. 5. Immunoaffinity purification of HLA. HLA was purified from PD concentrate on a Sepharose CL 6B–anti-HLA column. HLA and B_2M coeluted with the elution buffer (glycine HCl, pH 2.5) (see arrow). All other PD proteins failed to bind to the affinity column (tubes 0–40).

column, a solid-phase capture enzyme immunoassay was used (Fig. 6). Beads coated with monoclonal anti-class I antigen consistently captured class I antigen present in the 50-kd fraction and reacted with peroxidase-labeled anti-B_2M. Anti-class I-coated beads failed to capture class II antigen. No reaction to class I-coated beads was observed with the 11-kd fractions.

Beads coated with anti-B_2M and developed with peroxidase-labeled anti-B_2M (noncompeting epitopes) reacted with both class I antigen and B_2M (Fig. 7) in the 50-kd fraction. Free B_2M also was detected in the 11-kd fraction. These data show that HLA class I and B_2M antigens are complexed while HLA class II antigens are not, and B_2M also exists in free form with a molecular weight of 11 kd.

EVALUATION OF HLA-BETA2 MICROGLOBULIN ASSOCIATION

BEAD	ANTIGEN	ANTIBODY	ABSORBANCE
ANTI-CLASS 1	50 KD FRACTION	ANTI-CLASS 1	0.056
ANTI-CLASS 1	50 KD FRACTION	ANTI-B2M	1.654
ANTI-CLASS 1	50 KD FRACTION	ANTI-CLASS 2	0.087
ANTI-CLASS 1	50 KD FRACTION	BSA	0.025
ANTI-CLASS 1	11 KD FRACTION	ANTI-CLASS 1	0.043
ANTI-CLASS 1	11 KD FRACTION	ANTI-B2M	0.037
ANTI-CLASS 1	11 KD FRACTION	ANTI-CLASS 2	0.056
ANTI-CLASS 1	11 KD FRACTION	BSA	0.042

FIG. 6. Solid-phase ELISA to determine HLA B_2M association. Polystyrene beads coated with anti-class I captured class I antigen present in the 50-kd fraction from Sepharose CL 6B chromatography and was detected using peroxidase-labeled anti-B_2M confirming their association. No reactivity was observed with peroxidase-labeled anti-class I, anti-class II, or BSA. There were no reactions between anti-class I and the 11-kd fraction.

EVALUATION OF HLA-BETA2 MICROGLOBULIN ASSOCIATION

BEAD		ANTIBODY	ABSORBANCE
ANTIB2M	50 KD FRACTION	ANTI-CLASS 1	0.569
ANTIB2M	50 KD FRACTION	ANTI-B2M	0.236
ANTIB2M	50 KD FRACTION	ANTI-CLASS 2	0.021
ANTIB2M	50 KD FRACTION	BSA	0.034
ANTIB2M	11 KD FRACTION	ANTI-CLASS 1	0.022
ANTIB2M	11 KD FRACTION	ANTI-B2M	1.132
ANTIB2M	11 KD FRACTION	ANTI-CLASS 2	0.032
ANTIB2M	11 KD FRACTION	BSA	0.025

FIG. 7. Solid-phase ELISA to determine HLA B_2M association. Polystyrene beads coated with anti-B_2M captured class I and B_2M from the 50-kd fractions. Free B_2M was captured in the 11-kd fraction.

Neutralization of Alloantisera with Soluble Affinity-purified Class I Antigen

As shown in Figure 8, 75% of the antisera reactive to A(9)24 and 60% of the antisera reactive to B(5)52 were neutralized by soluble class I antigen from patient 1. Similarly 20% of the antisera to A2, 25% to A33, 60% to B(22)55, and 100% to Cw3 were neutralized by soluble class II antigen from patient 2. Several additional reactions demonstrated a onefold decrease in reactivity but were not scored as inhibited. Anti-DR sera were not neutralized (Fig. 8).

Effect of Soluble Class I Antigen on the MLC Reaction

The addition of soluble HLA class I antigen from the patient used as a stimulator cell for two unrelated responders virtually eliminated blast transformation in both cases (Figs. 9 and 10).

INHIBITION OF PATIENT HLA TYPING WITH AFFINITY PURIFIED SOLUBLE HLA

PHENOTYPE		% of ANTISERA INHIBITED	REACTIONS NEUTRALIZED
PT=1	A 1	0	0/4
	A (9)24	75	3/4
	B 8	0	0/4
	B (5)52	60	3/5
	Cw 7	0	0/1
	DR 2	0	0/6
	DR 3	0	0/6
PT=2	A 2	20	1/5
	A 33	25	1/4
	B (12)45	0	0/4
	B (22)55	60	3/5
	Cw 3	100	1/1
	DR 11	0	0/7
	DR 6	0	0/6

FIG. 8. Inhibition of anti-HLA alloantisera with purified HLA. Purified HLA class I partially inhibited reactivity of alloantisera directed against known alloantigens.

SOLUBLE HLA INHIBITION OF THE MLC REACTION

PATIENT HLA A2,(19)33/B(12)44,(22)55/DR 11,6

RESPONDER #1 HLA A3,(19)29/B7,40/DR12,(6)13

HLA CONC. ug/ml	C.P.M.	M.I.	%I
25.00	31.00	0.40	99.00
12.50	32.00	0.40	99.00
6.25	36.00	0.40	99.00
0.00	2951.00	34.00	0.00

FIG. 9. Effect of soluble HLA on the MLC reaction. HLA obtained from the stimulator cell donor completely inhibited blastogenic transformation in an unrelated responder cell 1.

Discussion

The presence of minute quantities of soluble HLA in human serum or plasma has been inferred since 1970.[3] For example normal human serum can neutralize anti-HLA serum.[3] Immunization with human plasma can induce the production of anti-HLA antibodies.[13] Nevertheless the technology to quantitate these molecules has not been available until recently.

The role of soluble HLA in body fluids remains unclear, but some studies have provoked considerable interest. A cell clone has been produced that secretes H-2 antigens without a cytoplasmic tail or transmembrane piece. Such H-2 antigens cannot attach to membranes. Similar H-2 antigens were then found naturally in rat serum and rat liver.[6]

In a series of experiments, Kamada and associates[7] found that liver transplants survived indefinitely between some histoincompatible rat strains. This was associated with circulating rat transplant antigens from the liver donor.[14]

We reported factors in the serum of a human liver recipient that suppressed mixed lymphocyte reactions between the recipient and donor.[15] Subsequently HLA of donor phenotype has been shown to appear in the serum of liver recipients almost immediately after liver transplantation.[5,16]

These observations led to suggestions that soluble HLA plays a role in maintenance of self tolerance,[6] prevention of autoimmune disease,[17] the rarity of hyperacute liver rejection,[16] and the tolerogenic effect of liver transplantation.[6]

Thus a better understanding of the biochemistry and physiology of soluble HLA seems important. Human lymphocyte antigen is present in the serum of all humans: concentrations seem relatively stable in individuals, but some people carry concentrations several times greater than others. The average levels are approximately 300 to 400 ng/mL (unpublished observations). These concentrations are so small that the various manipulations required for detailed study are very difficult. However the use of spent PD to recover soluble HLA should prove advantageous. Although the concentration per milliliter is similar to serum, the average patient on permanent peritoneal dialysis discards about 10 L of such fluid daily. By rather simple concentration and purification techniques, milligrams or even grams can be obtained.

A great deal of very basic information in this type of study remains to be gathered. For example it is not certain that all allotypes comprising an individual's phenotype are present in soluble form. Some evidence suggests that HLA-A9[18] and HLA-A24[18,19] may be secreted in larger quantities than other epitopes. The neutralization experiments presented here seem to support that concept because all antisera reacting with the cells of the soluble HLA donor were not equally neutralized. However that assumption is not yet justified because the reactivity of each antiserum was not standardized.

It was surprising to observe that the soluble HLA containing only class I antigen from the donor of the stimulator cell completely suppressed an MLC between that cell and a random responder. It has been thought that only class II HLA was required for stimulation of the blastogenic phase of the MLC. This observation was not due to differences in dilution, osmolarity, or pH, but again is preliminary because the specificity of the reaction has not been established adequately.

It is clear that the liver is one source of soluble HLA, but it is also clear that it is not the only source.[5] Some HLA probably comes from the breakdown of various cells. Because this material contains the transmembrane piece and the intracytoplasmic tail, it is, therefore, heavier. The chromatographic studies suggest that the bulk of material isolated was of the lighter species.

The essence of this study was to demonstrate a ready source of an almost-unlimited quantity of HLA class I

SOLUBLE HLA INHIBITION OF THE MLC REACTION

PATIENT HLA A2,(19)33/B(12)44,(22)55/DR 11,6

RESPONDER #2 HLA A3,(28)68/B7,(12)44/DR2,8

HLA CONC. ug/ml	C.P.M.	M.I.	%1
25.00	213.00	0.80	93.00
12.50	107.00	0.40	96.00
6.25	850.00	3.00	70.00
0.00	2781.00	10.00	0.00

FIG. 10. Effect of soluble HLA on the MLC reaction. HLA obtained from the stimulator cell donor completely inhibited blastogenic transformation in an unrelated responder cell 2.

antigen that can be used to clarify the role of soluble HLA in the biology of transplantation.

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DISCUSSIONS

DR. GIL DIETHELM (Birmingham, Alabama): The authors have made an important observation in that the peritoneal dialysate of patients with end-stage renal disease contains HLA classes I and II antigens and beta 2 macroglobulin.

They raise an interesting question, though, as to whether soluble HLA antigens in body fluids may play a role in immunologic tolerance.

I would like to ask three questions.

First have you had the opportunity to examine the peritoneal dialysate of patients after transplantation, and if so, does the fluid contain antigens of the allograft? In other words, the patient has a catheter in place; he is on CAPD. You know what the peritoneal dialysate antigen profile is, and then you get a transplant. Are the HLA antigens of the transplant present in the peritoneal dialysate?

Second do you think the HLA antigens found in the peritoneal fluid are transudate, coming from the intravascular space, or are these antigens sloughed from the peritoneal lining?

Third how might you use the purified HLA antigens from the peritoneal dialysate to achieve induction of adult tolerance?

DR. FRANK THOMAS (Greenville, North Carolina): I would like to make a few comments and follow up on Dr. Diethelm's comments regarding the use of this system in the future for the development of human tolerance.

Dr. McDonald has identified a large source of soluble HLA antigens that has potential for future application in transplant tolerance. Peter Medawar first noted that histocompatibility antigens in soluble form provide tolerogenic signals to the recipient; whereas aggregated antigens such as those obtained with Freund's adjuvant mixtures produced immunogenic signals.

Working in Dr. David Hume's lab in 1972, our group modified techniques for solubilizing histocompatibility antigens. As seen on this slide, we are able to demonstrate that the soluble antigens were quite effective in combination with limited immunosuppression in promoting allograft survival in animals.

I note also that the soluble antigen preparations were far more effective than the donor substance used most commonly clinically for inducing tolerance, namely, blood. These results were consistent with Medawar's hypothesis that solubilizing cellular alloantigens might increase their tolerogenic potential.

Finally, when we applied this system to a vascularized cardiac allograft model, we were able to show significant graft prolongation with soluble antigen preparations. These studies and others have led to optimism regarding the potential for induction of tolerance to soluble HLA antigen preparations.

Clearly one of the major objectives in this area is to obtain sufficient quantities of these antigens for tolerance induction.

Techniques that we use include three-molar KCL extraction and sonication potentially denaturing condition for membrane antigens.

The isolation of native soluble antigen, as done by Dr. McDonald here, presumably shed from the surface of cells, would be an attractive method for obtaining HLA antigens.

In this paper, Dr. McDonald may well have set the stage for the future application of techniques for inducing tolerance using soluble antigen preparations obtained from peritoneal dialysate.

I have three questions for Dr. McDonald.

John, do you have any idea as to whether a system of inducing tolerance with soluble antigens could be used after transplant or would require, instead, pretransplant conditioning of the recipient? Pretransplant conditioning of the recipient remains a significant logistic limitation for cadaveric transplantation.

Our early studies in dogs suggested that pretransplant conditioning of the recipient was necessary and, thus, this system may have limitations in human cadaveric transplantation. Do you see things that way?

Should pretransplant conditioning prove to be necessary, one way to apply this to the cadaveric situation would be to administer a 'cocktail' of class I and class II antigens that would cover the vast majority of potential HLA incompatibilities. Would this be an appropriate way to approach this problem?

What is your concept of the mechanism of the allogeneic unresponsiveness induced by soluble HLA antigens? Do the soluble antigens act to induce tolerance by eliciting idiotypic antibody responses, formation of soluble antigen antibody complexes that can block T-cell or K-cell function, or are there other mechanisms involved?

The paper represents an important contribution to our future attempts toward induction of stable transplant tolerances, as mentioned by Dr. Diethelm in the human, a sort of 'Holy Grail' of organ transplantation that has yet to be achieved.

DR. J. W. ALEXANDER (Cincinnati, Ohio): Dr. McDonald and his colleagues continue to advance the state of the art in transplantation research. The studies presented today reveal a ready and probably inexhaustible source of HLA antigen that might have many uses. These include a source antigen for production of monoclonal antibodies, a highly purified protein for sequencing and eventual production of large quantities of HLA antigen by recombinant technology, and production of large quantities of HLA antigen for studies in transplantation biology.

The last of these is perhaps of the most interest because many of us working in the transplantation field think that specific tolerance can be produced by the administration of donor antigens given in just the right way with immunosuppressive drugs before actual transplantation.

In fact recent studies have shown that the administration of donor antigen only 24 hours before the time of transplantation in concert with cyclosporin and/or other drugs may be an effective modality, leading to the possibility that this could be used in cadaveric transplantation.

They also may have an important role in desensitizing, if you will allow broad use of the term, patients who have existing antibody against HLA antigens.

I have only two questions. First why was there unequal distribution of neutralization of antisera reacting against the soluble donor HLA antigens in your studies? And second why did class I antigen totally suppress the MLC reaction?

DR. RANDY BOLLINGER (Durham, North Carolina): There has been a renewed interest among transplant surgeons and immunologists in humoral factors. We have that renewed interest because of the difficulty in transplanting our sensitized patients and the possibilities of xenotransplantation and tolerance induction for the future treatment of our patients.

Dr. McDonald and colleagues have found a humoral, that is, a soluble form of histocompatibility antigen that might be useful in several of these respects. But as Dr. Thomas has noted, you have to give the antigen at just the right dose, in just the right form. It can not be aggregated; it must be soluble. It must be given at the right time for it to work.

The fact that tolerance has these requirements raises certain questions that I would like to direct to the authors. The first of these is specificity.

You have shown in your paper an element of specificity for a particular donor and recipient. But to understand that this antigen is functioning in a specific immune way, we would have to see a panel of MLC reactions to know that, in fact, it would not have a similar effect in other MLC combinations. Do you have any data yet on other MLC reactions?

I have a question about concentration. Beta 2 microglobulin concentration varies with certain disease states, such as renal failure or urinary tract infection. Is there some variation in concentration of soluable histocompatability antigen seen in your patients when you tested this? Is the concentration of this soluble histocompatibility antigen in any way a predictor of immune responsiveness of the patients?

Would it, for example, in the post-transplant patient predict who would be likely to reject, as opposed to tolerate, the new graft?

I share the interest of Dr. Alexander in the MLC reaction. I wonder why this reaction that is ordinarily attributed to a class II antigen difference is so abruptly blocked by a soluble class I antigen.

DR. FRANK GELDER (Closing discussion): I have about five pages of notes to discuss, along with a very intriguing application for transplanters, and I would like to start with Dr. Diethelm.

Concerning the PD fluid itself, we have currently measured the HLA in some 40 or 50 patients; however, after transplantation, we have not examined the allospecificity of the fluid to determine if it is capable of coming from the kidney.

One piece of data that has been looked at frequently is out of Pittsburgh. This along with other groups who have looked at liver transplantation have shown fairly clearly that in the liver transplant patient or animal model that is under study, once they get past the surgery and the surgical problems associated with the transplant itself, the animal does very well.

Recently they have shown in humans that there is an allospecificity change after transplantation in which human sera of the recipient, both the recipient allospecificity and the donor allospecificity, are present.

We do not know whether the kidney carries that kind of mass. My theory is that based on the fact that kidneys continually need immunosuppression throughout their course of transplantation, there is not a large enough antigen load produced by the kidney to maintain the state of low-dose tolerance in the patient.

Where does the soluble HLA come from in PD fluid? I suggest that it is similar to that of albumin and comes from the bloodstream. Now if you recall our slides, in PD fluid we did have a small blip of HLA antigen with molecular weight in the neighborhood of 1,000,000 kd, one 1,000,000 daltons. That small blip may be from macrophages or lining cells in the peritoneal cavity itself; whereas the majority of the material had a 50,000-kd molecular weight. I theorize it is just transversing the capillary beds, as albumin would.

How would you use it to produce tolerance? Right now we are working on an animal model system. One of the things that is clear is that we can not get very large amounts of class I antigen using the monoclonal column that we are now using. The area that most intrigues us is producing clonal deletion using avenca alkyloid in conjunction with the soluble HLA or an I^{131} tracer with soluble HLA in an attempt to delete clonally.

In that fashion, one would not necessarily need to produce tolerance and maintain it for years or for the life of the graft.

The data scattered through the literature on clonal deletion is fairly sparse, principally because it has been fairly unsuccessful. That will be our initial thrust on using soluble HLA in these model systems.

Dr. Thomas you asked if soluble material can result in tolerance in the renal transplant. We do not know that now. We do not know the dose coming out, and we have not measured for that. In that system, though, we are working on it and we have four monoclonals to alloantigen domains in humans to show an alloantigen shift. What we need to have is not only a monoclonal to the backbone determinate but also monoclonals that effectively discriminate allospecificity between individuals. We just do not have that yet.

The mechanism of action of potential tolerance that is possible, I think, is a low-dose tolerance effect.

In particular in the liver recipients, low-dose tolerance could be maintained easily by the shedding of alloantigens from the donor. That has been shown to be the case in about 60% of the patients who have received liver transplants from one group.

Relative to the neutralization of the human alloantibodies that we are using, what we have looked at are both our in-house panels, pterosaki panels. And as you are probably aware, the strength of that typing serum varies tremendously. So an anti-A1 in one well may be ten times the concentration in anti-A1 in another well.

Initially we were pleased to see that the material that we had isolated had allospecificity that corresponded to some of the alloantigens of the donor. To do that experiment correctly, we need to obtain the appropriate alloantisera and block titrate it so that we can do effective neutralization based on chromicrogram HLA, regardless of the source from which it is coming.

Why did class I suppress MLC? As most investigators working in transplantation immunology know, the MLC is contributed principally to reactivity of class II antigens. We did not expect this reaction, but I could give you two or three guesses as to why it occurred.

We clearly get anti-class I both from T-cell and B-cell reactions in our patients, because we can measure them. We can measure an increase in blast transformation against these, as well as antibody production. But from the classic standpoint at this time, we do not have a definitive answer for that to explain the problem.

Dr. Bollinger, you are correct. We need to have additional data on other mixed lymphocyte culture reactions not only to define firmly the specificity of this reaction but also to define the dose of soluble HLA necessary to turn off the mixed lymphocyte culture reaction. We also need to obtain data relative to all HLA antigens equally as immunogenic, if looking at them in the MLC, or toleragenic if looking at turning off the MLC.

We have two additional experiments that duplicate this with MLCs but we do not have a complete battery as you suggested, although we are moving toward that.

We have some preliminary information regarding the soluble HLA class I in three conditions: normal, end-stage renal disease, and transplant patients. We do not have retrospective studies of our transplant patients to see what happens at the time of transplantation, out 1 year. These are random samplings at varying times within the first 3 to 6 months during the course of the transplant.

The end-stage renal disease patients we have not divided into categories of hemodialysis *versus* peritoneal dialysis. However, when we ran statistics on this, clearly ESRD and transplant patients are higher than normal, with a probability value of 0.05 or greater. So there may be some possibilities of using this as a predictor. Of course it is very early in its development.

Hopefully we can give you some additional data on how this can be effectively used, not only in disease monitoring but also in potential immunosuppression therapy next year.

I have answered your last question, Dr. Bollinger, relative to what is a block: the mixed lymphocyte culture. If you have any hypotheses on this, we would like to hear that.

Nonpalpable Invasive Breast Cancer

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The use of mammography has resulted in 1464 breast biopsies for nonpalpable abnormalities at the University of Virginia in the 10 years 1980 to 1989. Two hundred sixty-four cancerous lesions (18%) were found. One hundred seventy-eight of these (67%) were *in situ* lesions. Invasive cancer (86 of 264 lesions or 33%) forms the basis for this report. Mammographic findings leading to biopsy were a mass in 61 of 86 cases (71%), microcalcifications in 23 of 86 (27%), or both in 2 of 86 cases. Histologic subtypes were infiltrating ductal (63 of 86), infiltrating lobular (14 of 86), and other infiltrating (9 of 86). Mastectomy was performed in 71 of 86 lesions (82%), lumpectomy/radiation in 14 of 86 (16%), and lumpectomy alone in 1 of 86 lesions. Division of the tumors into size with nodal status revealed 19 of 86 lesions (22%) less than 0.5 cm with 0 of 14 positive nodes. Thirty-nine of eighty-six lesions (46%) measured 0.6 to 1.0 cm with 10 (26%) positive nodes. Twenty-eight of eighty-six lesions (32%) measured more than 1.0 cm with 8 of 28 (28%) positive nodes. Nodal status is unknown for eight patients. Overall 18 of 78 lesions (23%) had positive nodes. Median follow-up is 44 months. Disease-free survival rate is 92% (79 of 86 patients) and overall survival rate is 94% (81 of 86 patients). Six of seven recurrences occurred in node-positive patients. For those with negative or unknown nodes, the disease-free survival rate is 98% (67 of 68 patients). These findings emphasize the benefit of early detection of breast cancer through the use of mammography.

SCREENING FOR BREAST cancer by the use of mammography has resulted in the detection of an increased number of noninvasive cancers as well as the discovery of small invasive lesions. These nonpalpable invasive cancers unfortunately demonstrate a significant number of nodal metastases and therefore the term 'minimal breast cancer,' as described by Gallager and Martin in 1971,[1] should not be applied to these lesions. It is the purpose of this paper to evaluate a series of nonpalpable invasive breast cancers diagnosed at the University of Virginia from 1980 to 1989 and correlate the characteristics of tumor size, histology, and nodal status with outcome. Recommendations regarding management can be made as a result of this evaluation.

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Materials and Methods

Patients

From 1980 to 1989 at the University of Virginia, 1464 women had evaluation and biopsy of clinically occult nonpalpable breast lesions. All lesions were excised using Kopan's wire mammographic directed needle localization as previously described.[2] Two hundred sixty-four were malignant, with 177 (67%) of them determined to be *in situ* lesions (ductal carcinoma *in situ* or lobular carcinoma *in situ*). Invasive cancer was present in 86 patients (33%). These women with invasive cancer form the basis of this study.

Mammography and Pathologic Status

Mammography was performed for the entire study period with film screen techniques. Mammograms of all study patients were reviewed and the predominant finding leading to biopsy classified as a mass or density, clustered microcalcifications, or both. The pathologic status of all cases was reviewed to confirm the diagnosis of invasive cancer. Tumor size in this study is defined as the maximal diameter as measured grossly or histologically. Nine cases were excluded from detailed histopathologic analysis because the slides from these cases were unavailable for review.

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Follow-up

Follow-up status and treatment decisions were reviewed retrospectively. Data were obtained from hospital and physician charts and tumor registry information. Most of the patients are followed regularly in the Surgical Oncology Clinics at the University of Virginia (UVA). For those currently not followed at UVA, follow-up status was determined by direct patient and physician contact. Follow-up is expressed in months from initial diagnosis to date of last known contact.

Results

Patient Characteristics

Invasive cancer was present in 86 of 1464 (6%) nonpalpable lesions. Age ranged from 36 to 83 years (median, 62 years). Mammographic findings that prompted biopsy were clustered microcalcifications in 23 (26%), solid mass or density in 61 (71%), and both in 2 (3%) (Table 1). Local management of the breast was total mastectomy (simple or modified radical) in 71 (83%), wide excision plus radiation therapy in 14 (16%), and wide excision alone in 1. Wide excision plus radiation was used more widely in recent years. Axillary lymphadenectomy (level I/II) was combined with mastectomy or lumpectomy in 78 patients (90%). Factors leading to the decision not to perform axillary lymphadenectomy included advanced age, physician recommendation, and patient refusal.

Histology showed infiltrating ductal carcinoma in 63 patients (73%), infiltrating lobular in 14 (16%), and other infiltrating in 9 (10%). Tumor size ranged from 0.2 to 2 cm. Overall 18 of 86 women (20%) with nonpalpable invasive breast cancer had nodal metastases. Table 2 outlines the relationship of tumor size and nodal involvement.

TABLE 1. *Characteristics of 86 Patients with Nonpalpable Invasive Breast Cancer*

Characteristic	n
Mammographic finding	
Clustered microcalcifications	23
Mass/density	61
Both	2
Histology	
Infiltrating ductal	63
Infiltrating lobular	14
Other infiltrating	9
Local Therapy	
Total Mastectomy (simple or modified radical)	
Lumpectomy/radiation	71
Lumpectomy alone	14
Axillary dissection (with	1
lumpectomy or mastectomy)	78

n = 86.

TABLE 2. *Tumor Size and Axillary Nodal Status in 86 Women with Nonpalpable Invasive Breast Cancer*

Tumor Size	Number Total	Number of Axillary Dissection	Number of Positive Nodes
<0.5 cm	19	14	0
0.6–1.0 cm	39	36	10 (26%)
>1.0 cm	28	28	8 (28%)
Total	86	78	18 (21%)

Nineteen women had tumors less than 0.5 cm, of whom 14 had axillary dissection and none had nodal metastases. Thirty-nine women had tumors measuring 0.6 to 1.0 cm, of whom 36 had node dissection and 10 (26%) had positive nodes. All 28 with tumors larger than 1 cm had node dissection with 8 (28%) of them testing positive.

Follow-up

Follow-up ranges from 6 to 120 months (median, 44 months). Seventy-nine of eighty-six patients remain free of disease at last follow-up. Tumor recurred in seven women. Six of seven recurrences occurred in women with nodal metastases at the time of diagnosis. Time to recurrence from time of diagnosis ranged from 8 to 100 months (median, 14 months). Recurrence based on nodal status is outlined in Table 3. The disease-free survival rate for women with known negative or unknown axillary nodes is 98% (67 of 68 women) and for those with positive nodes the rate is 67% (12 of 18 women). The single disease event in the node-negative group was the development of a rapidly progressive contralateral new primary breast cancer 15 months after diagnosis of the original lesion.

Adjuvant therapy was not administered to most of the women with negative nodes. One premenopausal woman with negative nodes was treated with adjuvant combination chemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil) and four postmenopausal women received adjuvant tamoxifen.

Discussion

This study outlines the findings in a group of women with invasive breast cancer detected by mammography while the lesion was nonpalpable. The data raise a number

TABLE 3. *Follow-up Status for Women with Nonpalpable Invasive Breast Cancer*

Node Status	Total	Number Recurred	% DFS*
Negative	60	1	98%
Unknown	8	0	100%
Positive	18	6	67%

* Median follow-up, 44 months.

TABLE 4. *Relative Incidence of* In Situ *(LCIS or DCIS) and Invasive Cancers in Series of Biopsies of Mammographically Detected Clinically Occult Breast Lesions*

Study	n	*In Situ* Lesions (%)	Invasive Lesions (%)
Tinnemans[12]	151	34	66
Schwartz[13]	330	31	69
Papatestas[14]	149	40	60
Symmonds[15]	72	18	82
Univ. of Virginia*	264	67	33

* Reported in present series.

of issues including the effectiveness of mammography in reducing breast cancer deaths, the need to biopsy many benign lesions, and the treatment of these women, including the use of axillary dissection and adjuvant therapy.

The report by Egan[3] in 1960 spurred the increase of mammography for breast cancer detection, leading to the National Breast Cancer Demonstration Detection Project in the 1970s.[4] Long-term results showed that 42% of cancers in women older than 50 years were found by mammography alone and that the mortality rate was decreased by 27% for screened women. Other studies demonstrated a survival benefit for women who undergo periodic breast cancer screening, including Henson's[5] recent report of decreased mortality rate in women in the Bay area since 1973 attributed to screening. Smart[6] recently published a complete review of the role of mammography in breast cancer.

The detection of these cancers requires that many benign lesions be biopsied. The incidence of positive biopsies for suspicious mammographic findings ranges from 15% to 30%.[7] The high rate of negative biopsies has prompted some to question screening programs and cost-benefit studies have been recently presented.[8] Techniques to reduce the number of negative biopsies are under active investigation. The most promising is stereotactic localized fine-needle aspiration biopsy. Certainly the high rate of negative biopsies can be justified if there is improved outcome for women with mammographic-detected breast cancer.

Interestingly the high negative biopsy rate for nonpalpable lesions has seldom been compared to that of palpable lesions not amenable to cytologic evaluation. In our institution 1464 biopsies for suspicious mammograms yielded 264 cancers (18%). In the period 1988 to 1989, the positive-biopsy rate for palpable lesions not amenable to fine-needle cytology was 20%. Lay[9] reported a 15% positive-biopsy rate for palpable lesions at the University of Florida. Spivay[10] and Shapiro[11] reported similar findings.

Active breast screening has increased the number of cancers detected by mammography and has changed the distribution of cancer types. From 1968 to 1978, 4% of cancer at UVA were detected by mammography compared to 45% from 1988 to 1989. Of 264 nonpalpable cancers in this series, fully two third were *in situ* lesions. This compares to palpable lesions, of which 90% are invasive. Others have also reported a higher proportion of *in situ* lesions in recent series (Table 4). The preponderance of *in situ* lesions seen in our series may be explained by the 18% positive-biopsy rate compared to 29% to 31% in others.[12–14]

We found that most lesions that proved invasive appeared as a mass or density on mammogram. In many series clustered microcalcifications are the more common finding for malignancy. This difference may be due, in part, to the fact that this series only includes invasive cancers. *In situ* lesions are more consistently associated with microcalcifications. Many series of mammographic findings group invasive and *in situ* lesions together.

The histologic makeup of this series is not unusual, with 73% infiltrating ductal cancer. It is of particular interest that there is no difference in histologic type or nuclear grade in those lesions measuring less than 1 cm. This supports the notion that these are truly invasive cancers that differ from larger lesions in size only.

In this series 21% of women had nodal involvement. Other studies also report a significant incidence of nodal metastases in nonpalpable invasive breast cancer (Table 5). The incidence is 0% to 7% for lesions smaller than 0.5 cm and up to 25% for those measuring 0.6 to 1.0 cm. These figures demonstrate that invasive cancer can be found by mammography while it is small and localized to the breast. The data also emphasizes that small invasive cancers metastasize with distressing frequency and that invasive cancer cannot be labeled 'minimal breast cancer' on the basis of size alone.

Most of the women in this group were treated with mastectomy. Multiple factors entered into the decision process. The incidence of mastectomy for these small lesions is high but corresponds with other reported series.[14–17] Breast-conserving surgery was more broadly applied in the latter years of this series. Level I/II axillary

TABLE 5. *Incidence of Nodal Metastases in Women with Mammographically Detected Invasive Breast Cancer from Reported Series*

Study	Inclusion Criteria	n	Node Positive (%)
Schwartz[13]	Nonpalpable	167	33
Tinnemans[12]	≤0.5 cm	13	7
	0.6–1.0 cm	24	12
	≥1.0 cm	44	29
Ciatto[16]	≤1.0 cm	34	2
	≥1.0 cm	79	18
Univ. of Virginia	≤0.5 cm	19	0
	0.6–1.0 cm	39	26
	≥1.0 cm	28	28

dissections were performed in 90% of these women, with the findings outlined above. Because of the implications for postsurgical therapy and survival, and because the incidence of nodal metastases is significant, we endorse performing level I/II axillary node dissection in nonpalpable invasive breast cancer.

The survival of these women correlated with nodal status. With a relatively short median follow-up period of 44 months, 98% of those with negative or unknown nodes were disease free. Recurrence in 33% of women with positive nodes corresponds to expected figures for node-positive disease. This underscores the seriousness of the disease regardless of tumor size or method of detection.

The high disease-free survival (DFS) rate for node-negative or unknown nodal status women corresponds closely with other recently reported series. Tinnemans[12] and Ciatto[16] had 90+% DFS at 10 years. Carter[18] reported 98% 5-year DFS, Rosen[17] 86% 20-year DFS, and Rosner[19] 96% 7-year DFS. Node-negative women in general do worse in these series of small lesions. A recent analysis of node-negative breast cancer by Henderson,[20] including the control arms of randomized studies of adjuvant therapy, showed that 5-year DFS is only 65% to 75% for all node-negative women. Studies of adjuvant therapy have shown benefit for women with negative nodes who receive adjuvant therapy. The findings in this paper question whether data from these controlled series can be extrapolated to all women with node-negative invasive breast cancer. This study and others demonstrate that adjuvant therapy is not necessary for the subset of women with node-negative invasive breast cancer whose tumors are small and nonpalpable.

Summary

Mammographic screening for breast cancer detects nonpalpable invasive breast cancer as well as a high proportion of *in situ* lesions. Detecting cancer at this small size results in lower breast cancer mortality rates. The presence of axillary node metastases in more than 20% of women with nonpalpable invasive breast cancer supports the need for axillary dissection and emphasizes that this is not minimal breast cancer. The correlation of size and node status with excellent survival rates identifies a subset of women with node-negative breast cancer who are not candidates for adjuvant therapy.

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DISCUSSIONS

DR. JERRY M. SHUCK (Cleveland, Ohio): This presentation from the University of Virginia lends itself to comparison to other such surveys of mammographically discovered nonpalpable breast lesions.

Last month at the Western Surgical Association, we presented our experience with 1144 needle localization biopsies. We found an incidence of 25% malignancy rate, compared to this recently presented paper, in which the incidence was 18%. The authors noted that they have found that as well, and they think it will decrease for the rest of us.

If we are becoming more discriminating in whom we biopsy, why should that rate decrease? Our series showed that 75% of the cancers were invasive and 25% were *in situ*. This is similar to most studies.

Could explain why you only had a 33% incidence of invasive cancer *versus* 75% in most of the other series. Are we all talking about the same lesions? Do we have the same criteria?

You suggest that adjuvant therapy is not necessary even though the follow-up is short. Despite the fact that I really want to agree with that, do your data support that conclusion?

The correlation of pathologic findings with the x-rays may help plan management. Note on the slide that the calcifications are in younger patients. Those are generally not invasive cancers. Do they all need a biopsy? Is that the reason the rate is so low? Are we becoming so careful and perhaps even fearful that some of these are being biopsied?

This slide shows that although the benign calcifications occur in younger patients, age does not seem to affect the incidence of invasive cancer when a mass was seen. This is the mammographic finding of a mass, which has a high incidence of invasive cancers.

Do you have any other predictors from your mammographic experience? Recently we submitted data, which is not yet published, from a large series with long follow-up, all of whom had mastectomy. That study shows that even tumor size may not be as reliable a predictor for survival as we thought. That is because we corrected for node status, and we could not get probability values from a very large data base.

However your tumor sizes are subdivisions of nonpalpable lesions, which makes this even more interesting than our study and a unique aspect of your study.

I do look forward to the long-term follow-up of this important series.

DR. SHELTON HORSLEY (Richmond, Virginia): This is a wonderful example of what can be accomplished with really high-class, high-grade mammography, namely, the early detection of relatively small nonpalpable breast cancers, which for the most part have a very good prognosis. Dr. Wilhelm has very carefully noted that there is a significant incidence of regional node metastasis, even though these lesions are small. Therefore, a regional node dissection should be done.

The techniques for needle localization, we also use the Kopans wire. Originally we used the injection of methylene blue dye. We have not been completely satisfied with the Kopans wire, so we have asked our radiologists also to inject a blue dye. One of our bright radiobiologists checked the methylene blue and discovered, much to our surprise, that the methylene blue will cause a falsely low hormone receptor value in your cancer. We have switched to isosulfan blue which has no effect on the hormone receptor determination. We use both the Kopans wire and the dye and have been very satisfied.

I would also like to ask Dr. Wilhelm several questions.

Have you been able to study other parameters? Granted it is a small specimen, but have you been able to study these specimens to determine the estrogen receptor levels and also possibly flow cytometry? It is hoped that some of this will give us additional information that will help us determine whether these patients would benefit from adjuvant therapy.

Do you have any data with regard to the risk factors of these particular patients involved in this study? What percentage of these had a cancer of the opposite breast and which patients were at high risk, from the standpoint of family history, having a first-degree relative with breast cancer?

DR. MARSHALL URIST (Birmingham, Alabama): I would like to ask one of the same questions, that is, what is the ideal retrieval rate or ratio for positive diagnoses? Our positivity rate at UAB is also 26% and we are not sure if that is high enough. We would like to even make it higher and, of course, that places a burden on those who will follow lesions that are indeterminate.

Related to this, have there been any changes in the rate of positive responses over the years?

I understand that you are biopsing the same number of cases, but are you getting any smarter each year? Is your positivity rate increasing? We have not seen that change occur.

And, last, one of the differences related to *in situ versus* invasive lesions addresses an additional component of patients who benefit from this procedure, and that is those who have different forms of atypia. These women learn that they are at higher risk for the development of a malignancy and should be followed more closely. What is your percentage of patients who have this finding?

DR. ROBERT HUMMEL (Cincinnati, Ohio): One of the problems of being last discussant is that most of the points have been touched on, but I do want to add my voice to those who have congratulated Dr. Wilhelm for his interesting paper.

I would like to focus on the incidence of his stage 0 *in situ* lesions. It has been mentioned that the 67% rate is high, but it is about twice as high as any reports that I have seen in the past and is certainly higher than our rate.

This is an old slide that goes back several years, at which time we had about 33% stage 0 carcinomas, with an incidence of about 19% positive predictive value (PPV) on nonpalpable breast lesions discovered by mammography. At that time we thought this was a relatively high figure and a few people even wondered about our friendly pathologist.

When we looked at this 2 years ago, our figure was even a little higher. But we notice that our predictive value had decreased considerably, and this worried us. Since that time we have had the radiologist grade all of these lesions on a scale of 1 to 20, from benign to malignant, and have a much better idea about their real evaluation of these lesions.

Our data now has increased to 19%, but PPV stage 0 has decreased to about 32%. I will say that of our stage 0 lesions, we include those invasive tumors that are smaller than 0.5 cm, as many people do. So our figures, if we removed those lesions from our analyses, would be even lower and nowhere near the 67% rate.

Do you, Dr. Wilhelm, have any other explanation for the high incidence of stage 0 lesions? You have already mentioned the low percentage of lumpectomy irradiation done in these patients. Is that the choice of the patients? If they are offered both procedures, is there a significant trend toward doing more lumpectomy cases in these relatively small lesions?

And, finally, without getting into the whole question of treatment of minimal breast cancer, do you believe axillary dissections should be done on these very small lesions that measure 0.5 cm or so and show only one microscopic area of invasion?

There has been some sentiment lately that those patients have such a low, 1% or less, incidence of lymph node involvement that a node dissection is not necessary.

DR. STEPHEN EDGE (Closing discussion): Judging by the response from the audience, this is a process that we must all deal with on a daily basis and is becoming quite cumbersome to many surgeons.

Dr. Shuck told me earlier today about one of his faculty members who does seven to eight of these breast biopsies every Friday afternoon.

Dr. Shuck asked particularly whether, with our increasing discrimination on mammography, we are decreasing the number of negative biopsies. And I think this is a very important question because more and more women are having screening mammograms or more and more women are being forced to undergo invasive procedures of an open breast biopsy.

We are becoming somewhat more discriminating in that the last 12 months our positive rate has been 24%. However our overall series rate of 18% corresponds with that of other large series.

For instance the Scott White Clinic reported a positive rate of 14% in a large series presented at this Association in 1986.

Furthermore it is difficult to classify the degree of suspicion on mammograph criteria. And I think many of the different scales that have been suggested have failed to prove useful.

Furthermore a high positive rate is not necessarily good, in that potentially you will miss a large number of cancers by not biopsing relatively low-suspicion lesions. And we are fooled all the time in that a very high-suspicion lesion is benign and a low-suspicion lesion is malignant.

We need research to lower the number of negative biopsies that are done so that we minimize the number of operations that are done and, perhaps, convince more women to have screening mammography.

One technique that is under active investigation around the world, including at the University of Virginia, is the use of stereotaxic localized fine-needle aspiration cytology. This technique has been reported by the Swedes to allow biopsies to be done with an 85% positive rate with no breast cancers missed in the group that was not biopsied.

A number of discussants have asked, including Dr. Shuck, why we only had 33% invasive cancers. We do have a very high incidence of *in situ* lesions in this series. And, incidentally, those are approximately equally divided between lobular carcinoma *in situ* and ductal carcinoma *in situ*. And, therefore, we are including lobular carcinoma *in situ* as a malignancy.

I do not think we have any real explanation. It is double the rate of any other reported series in the literature that I have seen.

Dr. Shuck appropriately asked if our short follow-up data appropriately support the statement that these patients should not receive adjuvant therapy. We recognize that the short duration of the follow-up in this study is a serious drawback. We submitted this report because of the paucity of the data in the literature on small invasive cancers.

However we would like to point out that this length of follow-up is the same length of follow-up as reported on adjuvant trials by the NSABP in which 3- to 4-year disease-free survival was only 70%. Again we must qualify that by recognizing that with these very small lesions, recurrences might occur later.

In support of our findings, however, a number of recent reports of long-term follow-up of small T-1 lesions smaller than 1 cm, of 85% at 18 years by Rosen, 95% from an Italian group at 10 years, and 91% at 7 years by Rossener.

Unfortunately, Dr. Horsley, we are unable to evaluate other factors such as estrogen receptors or flow cytometry, and so on. During the period of the study, we are not doing immunocytochemistry on these lesions, and the flow cytometer was not available for the majority of this. And many of these lesions are so small that pathologists are afraid that they will destroy the ability to make the diagnosis at all, as, of course, you well know.

Also, it is very difficult in a retrospective study such as this to identify those risk factors, such as family history, that are important. None of these women had cancer in the opposite breast.

Dr. Urist, you asked what is the ideal retrieval rate, and I think I have addressed that question. It is very difficult to determine which women to biopsy. We are taking a very aggressive stance to diagnose very many early lesions. We do not know what the percentage of atypia is, at least I do not have that data with me.

The question of breast conservation surgery is an important one. We consider that breast conservation is the ideal for all women. Obviously it is not appropriate for every woman. Some women will choose mastectomy plus or minus reconstruction. Other women will perhaps not be ideal candidates for this, but we have moved very aggressively toward breast conservation, both in this group of women and in women with larger breast cancers. And there is clearly a trend in our data toward more broad use of breast conservation surgery in the last few years.

Axillary dissection gives important prognostic information. The presence of axillary node positivity makes these cancers no longer minimal breast cancer, and they must be treated as any other stage II breast cancer.

And for that reason we have taken the posture that women with these small invasive breast cancers should undergo level I and level II axillary lymph node dissection so we may eliminate adjuvant therapy for those women with negative nodes.

I do not think we can answer adequately the question of whether the specific subset of women with a tumor smaller than 0.5 cm should have lymph node dissection.

Stapled Ileoanal Anastomosis for Ulcerative Colitis and Familial Polyposis Without a Temporary Diverting Ileostomy

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Between March 1989 and August 1990, we performed 21 stapled J pouch ileoanal procedures (20 ulcerative colitis [UC], 1 familial polyposis [FP]) without an ileostomy in 19, of whom 13 were taking prednisone and eight underwent semi-emergent surgery for uncontrollable bleeding. During the same time, an additional four patients required a standard ileoanal procedure. The results of anal manometry and clinical function were compared to 25 patients who had previously undergone mucosal stripping and a sutured J pouch ileoanal anastomoses with a temporary diverting ileostomy between October 1982 and August 1990. During this same time period, an additional 19 patients underwent an antiperistaltic reversed J pouch and 18 an S pouch, for a total of 83 ileoanal procedures. The reversed J pouch had a lower stool frequency than a standard J pouch but had an unacceptable incidence of complications and problems with pouch emptying. The S pouch had a stool frequency similar to the standard J pouch but provided greater length in patients with a short mesentery. Stapled J pouch ileoanal patients had a better ($p < 0.02$) maximum anal sphincter resting pressure (46 ± 11 *versus* 34 ± 12 mmHg), fewer ($p < 0.05$) night-time accidents (22% *versus* 68%), daytime (17% *versus* 55%) or night-time (28 *versus* 61%) spotting, or use of a protective pad at night (11% *versus* 42%) than nonstapled J pouch ileoanal patients. Stool frequency was similar in the two groups. All but one UC patient had residual disease at the anastomosis. Anal mucosa between the dentate line and stapled anastomosis was 1.8 ± 1.3 cm (range, 0 to 3.5 cm). Complications in the nonstapled J pouch group included 4 pouches excised (2 for complications, 2 for excessive stool frequency), 1 pelvic abscess, 2 stenosis requiring dilation under anesthesia, 1 enterocutaneous fistula after ileostomy closure, 1 ileostomy site hernia, and 2 small bowel obstructions. Of the 65 patients who underwent ileostomy closure in the entire series, 8 (12%) developed a complication requiring surgical intervention. Complications in the stapled group included 1 anastomotic leak, 1 pouch leak, and 1 pelvic abscess. Patients were managed successfully with drainage (all 3) and diverting ileostomy (1). One patient developed stenosis requiring dilation under anesthesia. The stapled J pouch ileoanal anastomosis is a simpler, safer procedure with less tension than a standard handsewn J pouch but leaves a very small cuff of residual disease. It provides significantly better stool control and may obviate the need for an ileostomy with its complications.

ALTHOUGH THE ILEOANAL procedure originally was proposed by Nissen in 1933[1] and further evaluated by Ravitch and Sabiston[2] in 1947, it was not until the late 1970s that the procedure began to achieve clinical popularity.[3-5] Although children seem to tolerate a straight ileoanal procedure,[6] most studies have shown that construction of an ileal pouch is necessary to decrease stool frequency to an acceptable number in adults.[7,8] Martin and Fischer[8,9] initially demonstrated improved stool control when the anal transition zone was left intact with the mucosal stripping begun 1 to 2 cm above the dentate line. Recent British studies proposed that the ileoanal procedure can be done more safely and expeditiously, and provide significantly better stool control, using a stapled technique.[10-13] Kmiot and Keighley[12] suggested that the operation might be performed without a diverting, protective ileostomy, except in steroid-dependent patients. Our first stapled ileoanal procedure appeared to be similar to a low anterior resection, where a diverting ostomy is rarely used. Because an ileostomy and its subsequent closure also have been associated with significant risks of complications,[14] it seemed appropriate to perform the operation without a diverting ileostomy when the situation warranted it.

Materials and Methods

Total abdominal colectomy with a mucosal proctectomy and ileal pouch–anal anastomosis was initiated at

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the Medical College of Virginia in October 1982. As of September 1990 we had performed 83 ileoanal procedures. The operation was initially constructed using the J pouch developed by Utsunomiya[15] and popularized at the Mayo Clinic.[7,16] Because of problems with excessive stool frequency and incontinence in some patients with a standard J pouch, a reversed J pouch with an antiperistaltic 'spout' was constructed in 19 patients. The S pouch, developed by Parks et al.,[4] was used in 18 patients, especially if there was tension in bringing either the J pouch or reversed J pouch to the dentate line of the anal canal for anastomosis. Thus the handsewn ileoanal anastomoses included 25 J, 19 reversed J, and 18 S pouches.

As a result of the British studies demonstrating improved continence using a stapled ileoanal procedure with preservation of the anal canal,[10-13] all patients referred for total colectomy for ulcerative colitis or familial polyposis after March 1989 were considered for this operation. From this date to September 1990, 21 patients underwent the stapled ileoanal procedure, of whom 20 had ulcerative colitis and one familial polyposis. After the first case in which the operation appeared to be as safe as a standard low anterior resection, we decided to perform the procedure without a diverting, protective ileostomy when there had been no technical problems.

Nonstapled Operative Procedure

The total abdominal colectomy, mucosal proctectomy was performed in a standard fashion, with the rectum dissected toward the *levator ani* muscles from an abdominal approach and the mucosal stripping begun at the dentate line from the perineal approach.[7] In contrast to the stapled technique, no effort was made to expose the *levator ani* muscles. The rectum was not everted during this dissection and every effort was made to avoid excessive stretch or injury to the anal sphincter muscles. Before dissection the rectum was irrigated with 1000 mL 1% neomycin solution. Exposure for the mucosal dissection was aided with the use of Gelpi retractors placed perpendicular to each other at the anal verge and injecting the submucosal tissues with saline containing 1:100,000 epinephrine.

The ileum was transected immediately proximal to the ileocecal valve with an ILA-52® stapler (3-M Corp., St. Paul, MN). Each limb of the J pouch was 15 cm long and a side-to-side anastomosis constructed with several applications of the ILA-52 stapler (15 patients) or a two-layer, running 2-0 polyglycolic acid suture (10 patients). The pouch was anastomosed to the dentate line of the anal canal with several interrupted 2-0 polyglycolic acid sutures. A flat, 10-mm Jackson-Pratt® drain (American V. Mueller Corp., Chicago, IL) was placed on either side of the ileal pouch and brought out through stab wounds in both lower quadrants above the inguinal ligament. Each drain was removed when it produced less than 10 mL of fluid for two 8-hour nursing shifts or if a pelvic radiograph revealed it to have become displaced out of the pelvis into the general peritoneal cavity.

In an attempt to reduce stool frequency, an antiperistaltic reversed J pouch was constructed in 19 patients. A standard J pouch was constructed as described and the ileum transected 5 cm proximal to the pouch after the mesentery was divided as far proximally as possible. The pouch was rotated 180 degrees and anastomosed to the afferent ileum; the efferent ileum was anastomosed to the dentate line. This procedure required a greater mesenteric mobility than the standard J pouch. An S pouch was constructed in 18 patients either to study the effect of a greater pouch compliance on stool frequency (12 patients) or because it provided greater mesenteric length if a standard J pouch ileoanal anastomosis was under too much tension (six patients). The S pouch was handsewn with three 10-cm ileal limbs and 2 cm of efferent ileum anastomosed to the dentate line.

In all instances a modified loop ileostomy was brought out in the right lower quadrant with the functional stoma constructed using an everted Brooke technique and the nonfunctional stoma placed at skin level. The ileostomy was closed after a barium enema documented healing of the ileoanal pouch and there was no evidence of stricture or sinus tract at the ileoanal anastomosis. This ranged from 4 to 60 weeks, with a median of 7 weeks after the ileoanal procedure.

Stapled Operative Procedure

The total abdominal colectomy and proctectomy were performed in a manner similar to the nonstapled procedure, except that a meticulous effort was made to dissect the rectum down to the *levator ani* muscles. A Roticulator® 30 disposable surgical stapler (Auto Suture Co., Norwalk, CT), using 3.5-mm staples, was placed across the rectum as close to the *levator ani* muscles as possible; this was aided by pulling the rectum proximally and having an assistant push the perineum superiorly using a closed fist (Fig. 1). After closing the Roticulator® stapler, the operating surgeon donned an additional glove and inserted an index finger into the anal canal to be certain that the stapler was close to the anal verge (and dentate line). If it was not, additional dissection of the rectum was undertaken and the above maneuvers repeated until its placement was considered satisfactory.

The J pouch was constructed with two 15-cm limbs using two applications of an ILA-100® (3-M Corp.) stapler placed through the apex of the pouch (Fig. 2). A 2-0 polypropylene purse-string suture then was placed at the apical opening of the J pouch and the anvil of the disposable Premium CEEA® 31 (Auto Suture Co., Norwalk, CT) was inserted within the pouch and the purse-string suture tied

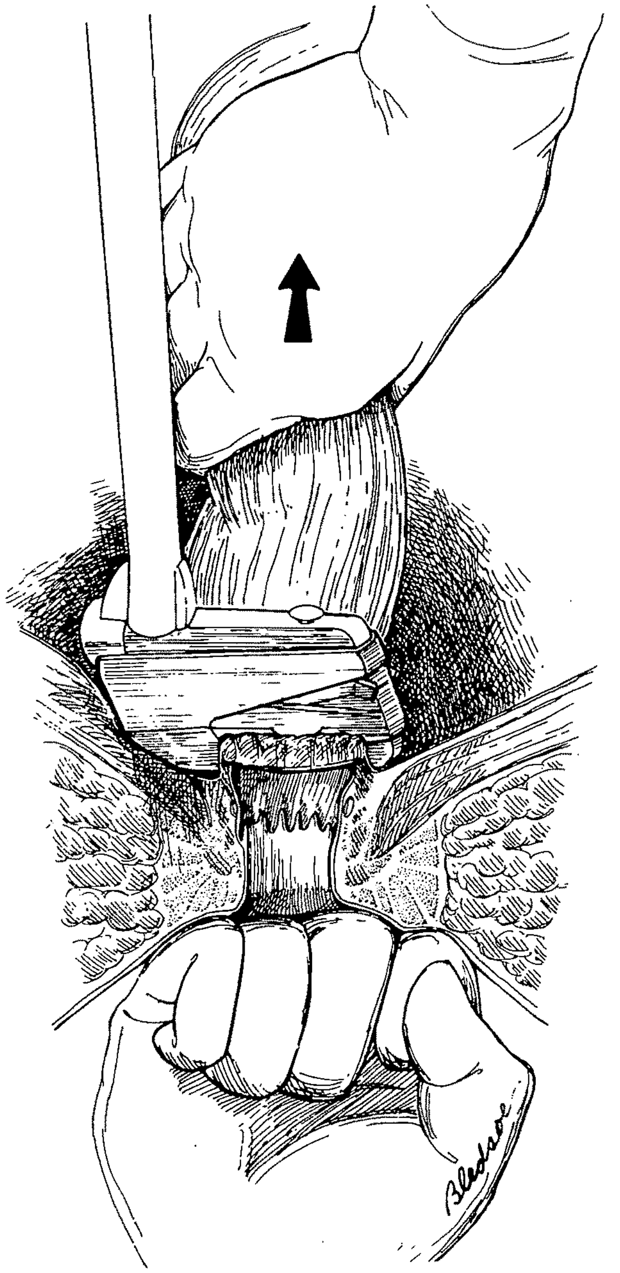

FIG. 1. Roticulator® 30 stapler with 3.5-mm staples placed across the rectum as close to *levator ani* muscles as possible with the rectum pulled proximally and the perineum pushed superiorly.

down. A Premium CEEA® 28 stapler was used in the first patient but subsequent experience documented that a 31-mm stapler could be used routinely if a sufficiently large opening was made in the apex of the J pouch.

The Premium CEEA® 31 was placed into the anal canal with the needle inserted on the central bar but retracted into the stapler. The needle then was advanced, taking care to place it through or as close to the Roticulator® 30 staple line as possible (Fig. 3). The needle was removed and the CEEA® 31 anvil within the J pouch connected to the CEEA® 31 stapler, taking care to bring the J pouch into the pelvis without twisting (Fig. 4). The CEEA® 31 stapler was closed and fired once, as hard as possible, when the green dot was visualized in the handle (Fig. 5). The CEEA® 31 handle was unscrewed three full turns and the stapler firmly, but gently, removed. This was difficult at times because four rows of staples (one on either side of the J pouch and one on either side of the anal stump) were crossed and transected with the CEEA® 31 instrument. The CEEA® 31 then was examined for intact 'doughnuts,' taking care to do so before removing them from the instrument, because the doughnuts will pull apart with excessive traction at the staple lines. The doughnut on the anal side of the anastomosis was routinely sent for pathologic examination. The ileal mesentery usually was taughtly applied to the retroperitoneal tissues. The mesentery was sutured to the posterior peritoneum in one patient to prevent an internal hernia. Jackson-Pratt® drains were placed as in the nonstapled ileoanal patients.

A #28 red rubber tube then was inserted into the ileal pouch from below and 100 to 200 mL saline darkly colored with methylene blue were instilled with the afferent limb digitally occluded, searching for leaks at the ileoanal or the J pouch anastomoses. An adult-sized sigmoidoscope then was inserted to evaluate the anastomosis and to measure its distance from the dentate line.

After our first case using the stapled technique, a diverting ileostomy was not constructed if the ileoanal or J pouch anastomoses were considered to be perfect. Furthermore no nasogastric tube was inserted unless the patient developed postoperative abdominal distension or nausea and vomiting. Once the patient began passing flatus, the diet was rapidly advanced: warm clear liquids followed by a general diet the next day and discharged the following day. The median postoperative hospitalization was 9 days.

If the stapling technique was not feasible for anatomic or technical reasons, a standard mucosectomy was performed and the ileal pouch anastomosed to the dentate line with interrupted 2-0 polyglycolic acid sutures. The ileal pouch was not constructed until it was determined whether a J pouch could be anastomosed without excessive tension; if not a hand-sewn S pouch was constructed because it provided greater length.

Measurement of Anal Sphincter Pressures

Anal manometry was performed with a pneumohydraulic capillary perfusion system, using a Statham® pressure transducer (Gould Inc., Oxnard, CA) connected to a Hewlett Packard® recording system (Palo Alto, CA). A triple lumen poly-vinyl catheter with an external diameter of 4.8 mm was used with two orifices located 3 cm apart and positioned radially in the axis of the two. The per-

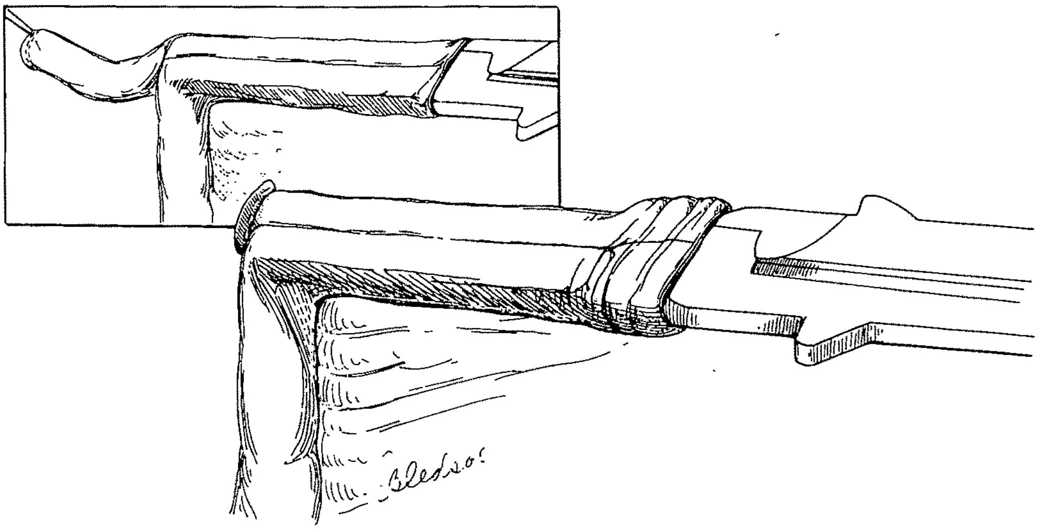

FIG. 2. Construction of J pouch with 15-cm limbs using two applications of ILA-100® stapler.

fusion rate was 0.5 mm/minute. The central lumen was attached to a balloon with a 150-mL maximum volume, which was used to distend the ileal pouch. The catheter was passed into the pouch and withdrawn through the anal sphincter using the standard pull-through method with the orifices positioned to record the maximum resting pressure of the anal sphincter. The patient then was asked to voluntarily squeeze the anal sphincter and maintain the squeeze for as long as possible. The balloon was inflated and deflated in increments of 10 mL of air and the patient asked to report the onset of rectal sensation during incremental distention. The resting sphincter pressure was defined as the mean of the resting pressures from each port during two successive station pull-through. With the catheter positioned in the sphincter to record the maximum resting pressure, the mean of three successive maximum squeeze pressures was recorded.

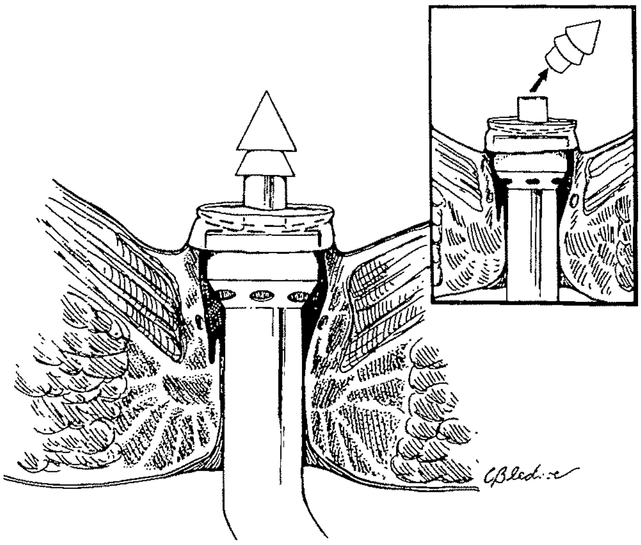

FIG. 3. Insertion of the Premium CEEA® 31 stapler through the anus with the needle passing through the rectal cuff as close to the Roticulator® staple line as possible. Insert shows removal of the detachable needle from the CEEA® 31 stapler.

Patient Questionnaire

Patients were sent a questionnaire by mail and asked to return the completed form to the nurse practitioner. Questions relevant to this report included the most, least, and average number of daytime stools; the most, least, and average number of night-time stools; the number of accidents during the day or night; the frequency of spotting (defined as soilage the size of a quarter) during the day or night; the need to wear a perineal pad; and the necessity of using medications such as Immodium® (McNeil Consumer Products, Ft. Washington, PA) or powdered fiber supplements (*e.g.*, Metamucil® [Procter & Gamble, Cincinnati, OH]) to thicken the stool.

Evaluation of Postoperative Rectal Bleeding

All patients who complained of postoperative bloody diarrhea underwent outpatient examination with a rigid pediatric sigmoidoscope or disposable anoscope. Pouchitis was defined as bloody diarrhea associated with inflammation of the ileal pouch, which responded to oral antibiotic therapy with either metronidazole 250 mg twice daily or Bactrim-DS® twice daily. Residual ulcerative colitis of the anal canal was defined as inflammation (friable, bleeding tissue) of the anal canal between the dentate line and the anastomosis in the stapled ileoanal patients.

Data Analysis

All data are expressed as mean ± standard deviation and were analyzed by analysis of variance using the Statistical Analysis System (Cary, NC) program. Percentage differences between patient groups were compared using Fisher's exact test. A difference was considered significant at $p < 0.05$.

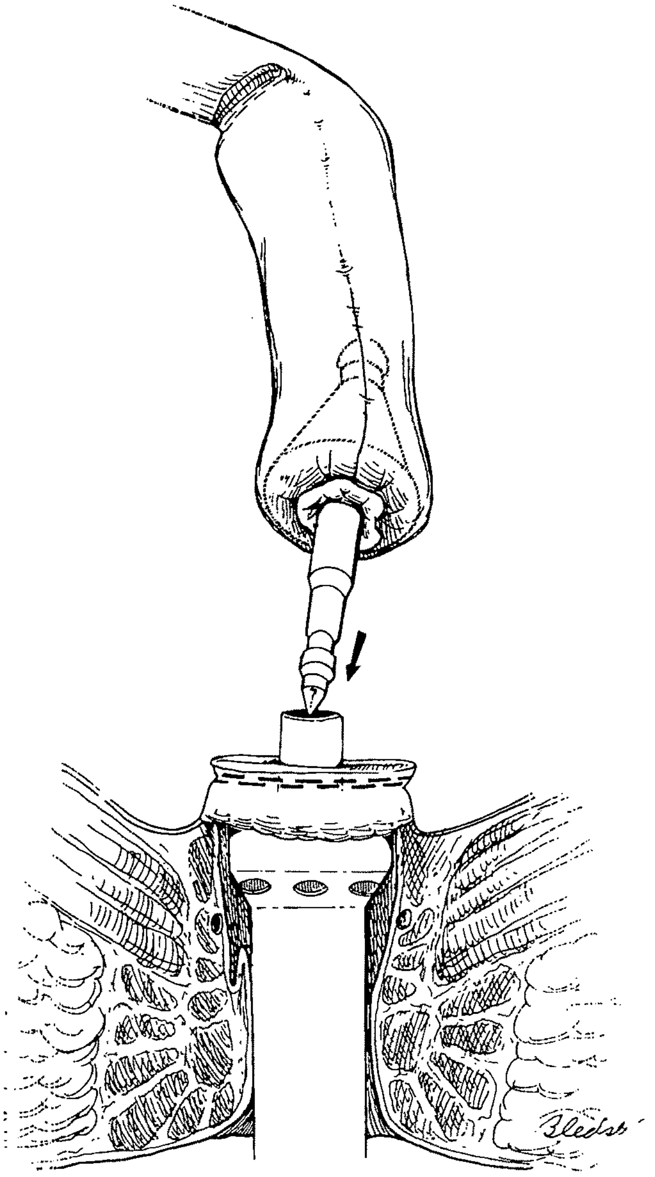

FIG. 4. Connection of the J pouch to the anus with the Premium CEEA® 31 anvil held in the pouch with 2–0 polypropylene purse-string suture.

Results

Although the antiperistaltic reversed J pouch provided significantly less stools per day than a standard handsewn J pouch (4.8 ± 1.8 *versus* 7.0 ± 3.3, $p < 0.05$), it had an unacceptable incidence of problems with evacuation and the need for pouch catheterization to achieve adequate emptying, as well as a number of serious complications, which in two instances were life threatening (Table 1). For these reasons the reversed J pouch procedure was abandoned. Stool frequency with the S pouch (8.1 ± 3.6) was not significantly different than the standard J pouch. Furthermore five of the S pouch patients also needed to use a silastic catheter to achieve adequate evacuation. Therefore the S pouch was used only when a J pouch provided inadequate length.

As of March 1989, all patients were considered to be candidates for the stapled ileoanal procedure with preservation of the anal canal. In two patients the operation could not be performed because the Roticulator® 30 instrument could not be placed below pre-existing diseased tissue, a large polyp in one patient with familial polyposis and a rectovaginal fistula in a patient with ulcerative colitis. The stapled technique had to be abandoned in two patients because of technical complications, disruption of the Roticulator® 30 staple line during insertion of the CEEA® instrument per anus and injury to the anal canal at the level of the *levator ani* muscle that prevented application of the Roticulator® stapler. In each of these four patients, a mucosal stripping to the dentate line was performed with a hand-sewn ileoanal J pouch in one patient and S pouch in three obese patients, because of the need for additional length. Ileoanal anastomotic tension was never a problem when the stapled technique was used.

Stool Control

The stapled ileoanal J pouch patients had significantly better maximum resting anal sphincter pressures (Fig. 6) and stool control (Fig. 7), especially at night (Fig. 8), than did those who underwent mucosectomy and a sutured ileoanal anastomosis at the dentate line. There were no differences in mean or maximal squeeze pressures between

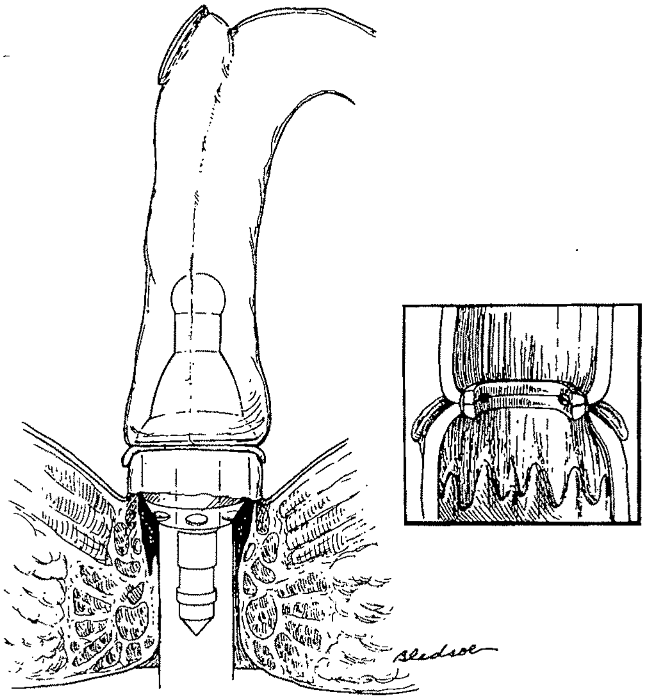

FIG. 5. Completed stapled ileoanal anastomosis. Insert shows the proximity of anastomosis to the dentate line.

TABLE 1. *Complications After Ileoanal Anastomosis*

Complication	Stapled J (n = 21)	Nonstapled J (n = 25)	Reversed J (n = 19)	S (n = 18)
Cuff abscess, sinus tract, leak	2	2	2	3
Pouch–buttock fistula	1*	—	2	1
Pouch–vaginal fistula	—	—	—	2
Pelvic abscess	1	1	1	1
Stenosis	1	2	2	3
Small bowel obstruction	—	2	1	—
Pouchitis	4	5	4	4
Inflammation of the anal canal	3	—	—	—
Pouch removed	—	4	1	1

* Occurred in same patient who had an anastomotic leak.

the two groups. None of the sutured patients and only one of the stapled patients had receptive relaxation noted with anal manometry. This was our first patient, who had the longest residual anal canal (3.5 cm) in the series. There were significantly fewer accidents or spotting at night in the stapled group and only one stapled patient wore a perineal pad at night, in contrast to 42% of the nonstapled patients (Fig. 8).

Stool Frequency

There was no significant difference in stool frequency between the two groups. The usual numbers of stools per 24 hours were 7.0 ± 3.3 (5.3 ± 2.6 in the day, 1.6 ± 1.5 at night) in the nonstapled group and 7.9 ± 2.6 (5.8 ± 1.8 in the day, 2.1 ± 1.4 at night) in the stapled group. There were also no significant differences between the two groups in the most (12.0 ± 4.2 nonstapled *versus* 13.1 ± 4.4 stapled) or least (4.5 ± 2.1 nonstapled *versus* 5.0 ± 1.9 stapled) total number of stools per day. More of the stapled patients (50%) than nonstapled (20%) patients were taking Imodium® to decrease stool frequency ($p < 0.05$). Approximately one half of each group were using Metamucil® to thicken the stool. The slightly increased number of stools and greater use of Imodium® in the stapled group may have been due to the shorter time interval between their surgery and assessment as compared to the nonstapled group, in which some of the patients had undergone surgery up to 8 years previously.

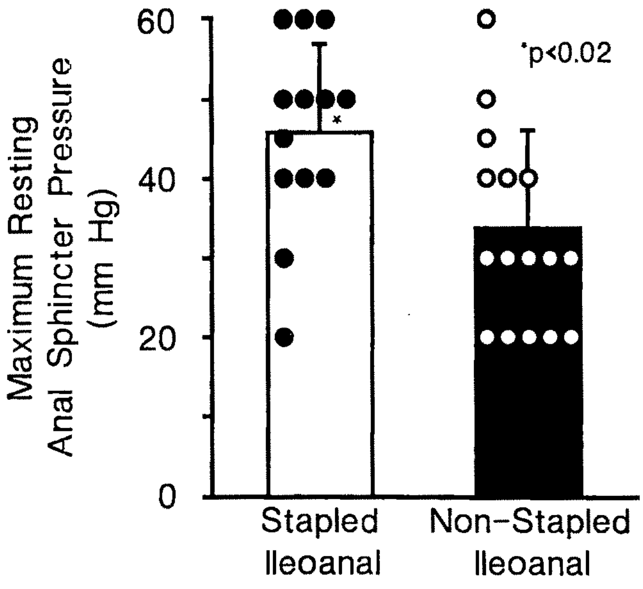

FIG. 6. Bar graph demonstrating significantly higher maximum resting anal sphincter pressure with stapled anastomosis (n = 13), as compared to mucosectomy with ileoanal anastomosis sutured at the dentate line (n = 16).

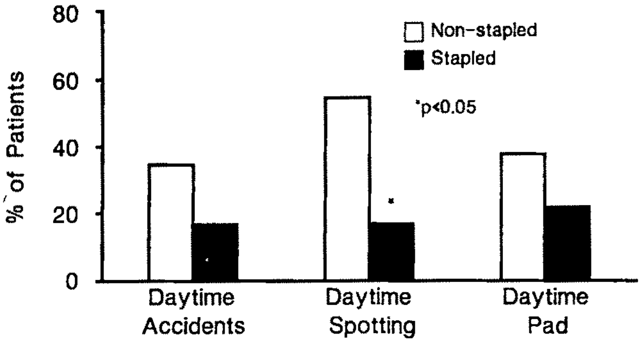

FIG. 7. Bar graphs demonstrating only significantly less daytime spotting with stapled anastomosis as compared to mucosectomy with J pouch sutured to the dentate line.

Residual Disease

Every attempt was made to dissect the rectum as close to the *levator ani* muscle as possible in the stapled group. This technique improved with experience. In the first patient, the distance between the dentate line and the anastomosis was 3.5 cm. All but one patient had evidence of residual disease in the anal canal at the anastomosis, as

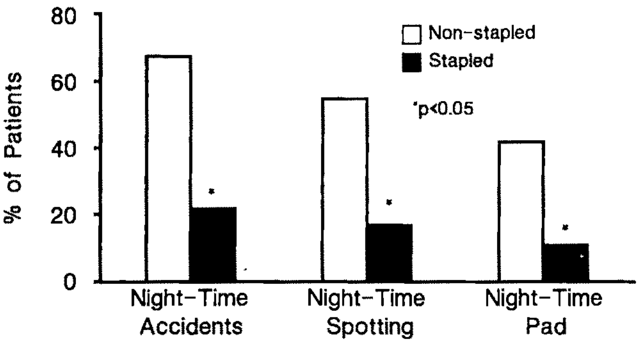

FIG. 8. Bar graphs showing significantly better night-time stool control with stapled ileoanal anastomosis as compared to mucosectomy with J pouch sutured to the dentate line.

noted both by pathologic examination of the anal 'doughnut' and by anoscopy. The length of the anal canal between the anastomosis and the dentate line measured at postoperative anoscopy averaged 1.8 ± 1.3 cm (range, 0 to 3.5 cm).

Three patients had symptoms attributable to acute inflammation in the diseased anal canal. This lasted approximately 6 months in one patient, responded to 0.5 steroid enema twice daily, and has been in remission for the past 12 months. The other two patients' symptoms of bleeding and burning were relieved with 0.5 Rowasa® (Reed-Rowell, Marietta, GA) enema daily. Each of these patients had severe refractory ulcerative colitis with bleeding before their stapled ileoanal procedures. The five other patients who underwent the stapled ileoanal procedure for fulminant colitis have not had symptoms attributable to inflammation of the anal canal.

Stapled ileoanal procedures were performed for three patients with severe dysplasia; mild dysplasia was noted at the margin of the anastomosis in one of these patients. There was no evidence of dysplasia in the rectal 'doughnuts' of the other 20 stapled ileoanal patients.

Pouchitis

Four of the stapled ileoanal patients have had symptoms of pouchitis (Table 1) that were associated with inflammation of the ileal pouch on endoscopy and responded to metronidazole (250 mg twice daily) in three and Bactrim-DS® (Roche Laboratories, Nutley, NJ) twice daily in one; one of these patients requires metronidazole therapy on alternating 2-week intervals for recurrent symptoms of pouchitis. Five of the nonstapled ileoanal J pouch patients have developed pouchitis (Table 1); all have responded to metronidazole or Bactrim-DS®. One patient has had frequent, recurrent episodes necessitating antibiotic therapy on alternating 2-week intervals for the past 4 years.

Ileostomy Use and Complications: Stapled Group

The procedure was performed without a covering ileostomy in all but 2 of the 21 patients. They were the first patient who underwent the procedure and the 14th patient, in whom a leak was identified at the anastomosis after instillation of methylene blue. Each of these patients subsequently underwent ileostomy closure after a barium enema demonstrated satisfactory healing of the pouch and the ileoanal anastomosis.

Of the patients who did not have fecal diversion, 13 were taking prednisone, and eight underwent semi-urgent surgery for uncontrollable bleeding. One of these patients also was severely malnourished (albumin, 2.2 g/dL) and developed a leak at the ileoanal anastomosis on the fourth postoperative day manifested by fever, tachycardia, and abdominal pain (Table 1). He underwent emergency construction of a diverting ileostomy and abdominal irrigation with a subsequent uneventful recovery. An abscess developed in his right buttock, which was drained and noted to communicate with the ileoanal anastomotic disruption. The fistula appeared to resolve with local wound care and the anastomosis appeared intact on barium enema so that the ileostomy was closed. Six months later the ileoanal pouch–buttock fistula recurred, with periodic drainage of gas and stool, refractory to local wound care, and necessitating ileostomy reconstruction and surgical debridement of the fistula.

The one patient with familial polyposis who had undergone the stapled technique developed a leak from the stapled J pouch itself (not the ileoanal anastomosis) immediately after removal of a Jackson-Pratt® suction catheter, which was manifested by severe pain and stool noted in the remaining suction catheter. The patient was explored, but severe adhesions prevented construction of an ileostomy. The patient was fed with total parenteral nutrition with subsequent healing of the pouch fistula. A third patient with ulcerative colitis, but which was not steroid dependent, manifested a pelvic abscess 3 weeks after the stapled ileoanal procedure. At the time of reexploration, methylene blue was inserted per anus into the ileoanal pouch and no leak could be detected. The abscess was drained and subsequently the patient has had no further complications in the 1.5 years since surgery.

One of the patients in the stapled J pouch group initially had excessive stool frequency, problems with leakage, and the need to wear a perineal pad. This patient had the lowest anastomosis in the entire stapled group, constructed at the dentate line. Anal manometry revealed a very low resting pressure but a good 'squeeze' pressure. During the course of 1 year, the patient gradually developed better stool control; however he still has frequent accidents and is the only patient who needs to wear a perineal pad at night.

Complications: Nonstapled Group

In the nonstapled J pouch group, two patients required removal of the ileoanal pouch because of excessive stool frequency and inadequate control (Table 1). The pouch was removed in two other patients as a result of complications early in the series: one from bleeding from pelvic veins and one from bleeding at the ileostomy anastomosis, which was treated at another hospital with radiographic bead embolization leading to subsequent necrosis of the ileoanal pouch. One patient developed a pelvic abscess that required drainage. Two patients required dilation of ileoanal anastomotic stenoses (Table 1). One patient in the standard J pouch group developed an enterocutaneous fistula after ileostomy closure (Table 2). There were three other enterocutaneous fistulas in the series after ileostomy closure: one with a reversed J pouch and two with an S

TABLE 2. *Ileostomy Complications*

Complication	Nonstapled J	Reversed J	S	Stapled J*
No. Patients	25	19	18	2
Enterocutaneous fistula	1	1	2	—
Ileostomy anastomosis bleed	1	—	—	—
Ileostomy anastomosis disruption	—	1	—	—
Ileostomy site hernia	—	1	1	—

* Nineteen patients underwent a stapled J pouch without ileostomy. Eight of sixty-five patients had ileostomy-associated complications.

pouch. Two patients developed ileostomy site hernias. Thus 8 of 65 patients (12%) who underwent ileostomy closure developed complications that required surgical intervention (Table 2). Three patients developed small bowel obstructions requiring laparotomy and adhesiolysis; two of these were in the standard J pouch group (Table 1).

Discussion

This study confirms the results of several British series[10-13] that after a total abdominal colectomy, an ileal pouch–anal anastomosis stapled immediately above the *levator ani* muscles is a procedure that is technically much easier and provides significantly better stool control than an ileoanal anastomosis sutured at the dentate line after a mucosectomy. During development of the ileoanal procedure, it was initially thought that the entire rectal muscular cuff was required to preserve adequate sensation for control of defecation.[4] However placing an ileal pouch within this long rectal cuff was associated with a high incidence of pelvic sepsis.[4] Shorter and shorter amounts of rectal muscle were preserved and the technique of mucosal stripping was performed entirely from the perineal direction to just above the *levator ani* muscle. No deterioration in anal sphincter function was seen and a lower incidence of pelvic sepsis was achieved.[5]

Stool Control

Martin and Fischer[8] were the first to note improved stool control after preservation of the columns of Morgagni above the dentate line, often called the anal transition zone. Significantly better anal sensation and discriminatory function also were noted by Holdsworth and Johnston[17] after a sutured end-to-end ileoanal anastomosis with preservation of the anal transition zone than after mucosal proctectomy with endoanal anastomosis. A similar improvement in anal sensation after preservation of the anal transition zone, which was not clinically significant, also was noted in a small series of patients by Miller et al.[18] On the other hand, Keighley et al.[19] did not find any impairment in discrimination after excision of this zone; however only six patients were studied who had the anal transition zone preserved in contrast to 15 who had it excised. Lavery et al.[20] also noted a significantly greater resting anal sphincter tone with better stool control with the stapled ileoanal technique. This group also noted that 50% of their patients had preservation of the rectoanal inhibitory reflex. Even a straight ileoanal anastomosis without construction of a pouch was associated with perfect anal continence when a mucosal cuff was preserved, as contrasted to a 30% incidence of significant incontinence after mucosectomy.[21] Our patients also had significantly better maximal resting anal sphincter pressures (Fig. 6) and stool control (Fig. 7), especially at night (Fig. 8), when the anastomosis was constructed at the *levator ani* muscles, thus preserving the anal transition zone, as compared to an endoanal mucosectomy with the anastomosis at the dentate line. In contrast to the study by Lavery et al.,[20] only one of our stapled ileoanal patients had evidence of receptive relaxation, or preservation of the rectoanal inhibitory reflex.

Risk of Persistent Disease Activity

The greatest concerns with procedures that preserve any tissue above the dentate line are the potential problems for continued disease activity and the possibility of malignant transformation. In the comments after a recent series reported using the stapling technique, it was stated that no residual diseased mucosa was left.[22] This is the group, however, who noted receptive relaxation in 50% of their patients,[20] a finding we only found in one patient and he had the longest (3.5 cm) residual anal canal. In our series residual ulcerative colitis was noted microscopically at the anastomosis in all but one of our stapled patients. Three of the stapled patients had problems with rectal bleeding and burning, which were controlled with small amounts of either a steroid or Rowasa® enema. It is certainly possible that other patients in whom we have performed this procedure could develop disease reactivation in the future. Bloody diarrhea in these patients can be secondary to either pouchitis or inflammation of the residual anal canal. Pouchitis has been thought to be secondary to overgrowth of anaerobic bacteria within the ileal pouch and usually responds to antibiotic therapy with either metronidazole or Bactrim-DS®.[23] Four of our stapled ileoanal patients developed symptoms of pouchitis that have responded to antibiotic therapy, an incidence that is not different from the nonstapled patients.

In a recent report from the Mayo Clinic, Lohmuller et al.[24] noted that extraintestinal manifestations of inflammatory bowel disease were frequent after the ileoanal procedure. This incidence was even greater in the patients who developed pouchitis. It is possible that leaving behind a small amount of diseased tissue might further increase the risk of extraintestinal complications, such as pyoderma gangrenosum, erythema nodosum, arthritis, uveitis, and so on. None of the stapled ileoanal patients in our series developed extraintestinal manifestations of inflammatory bowel disease to date.

Risk of Carcinoma

The greatest reservation for using the stapled procedure is the potential for malignant transformation of residual diseased anal mucosa. In one study an unsuspected adenocarcinoma of the anal canal, extending to the level of the dentate line, was found in a patient who was undergoing an ileoanal procedure for moderate dysplasia.[25] These authors believe that 'the anal mucosa should always be removed down to the level of the dentate line in restorative operations for ulcerative colitis.'[25] Stern et al.[26] recently reported a patient who developed an adenocarcinoma in the rectal cuff 4 years after a mucosal proctectomy and ileoanal J pouch for severe dysplasia; this patient had undergone a subtotal colectomy, ileorectal anastomosis 7 years previously at which time an occult, Duke's C adenocarcinoma was found in the ascending colon. These authors also believe that a radical total mucosectomy is mandatory in patients with ulcerative colitis. In one of our three patients who underwent the procedure for severe dysplasia, mild dysplasia was noted at the anastomosis. This patient had only 3 mm of residual diseased mucosa left below the anastomosis. In a study by Emblem et al.,[27] it was noted that 10 of 13 patients with familial polyposis with preservation of the anal transition zone developed further polyposis in this area.

Until recently ileorectal anastomosis often was used by colorectal surgeons for ulcerative colitis as an alternative to total colectomy, proctectomy, and permanent ileostomy. In one recent report of 51 patients with this procedure performed between 1955 and 1984, no patient developed a rectal carcinoma.[28] Khubchandani et al.[29] noted three adenocarcinomas (one *in situ*) in 51 patients for a 5.6% incidence. This is similar to the incidence noted in several published series, although the cumulative risk may be as high as 15% during a period of 30 years.[30–33] The risk of developing a carcinoma when leaving 1 to 2 cm of disease must surely be a fraction of the ileorectal experience, in which approximately 15 cm of diseased rectum was usually left behind.

It will, therefore, be incumbent on surgeons who leave the anal transition zone intact to inform their patients of the necessity for follow-up examinations of the anal canal. The frequency of these examinations is difficult to determine, but should probably be annually at first until the safety of the procedure can be established. The procedure will only require anoscopy, which would be far less costly, unpleasant, and time-consuming than a complete colonoscopy, to which these patients were previously subjected. A small commercial enema would be the only preparation required. Malignant transformation probably would necessitate an abdominal-perineal resection. This should be an integral component to preoperative informed consent.

Safety of the Stapled Ileoanal Procedure

The development of the Premium CEEA® and Roticulator® surgical intestinal staplers greatly simplified the operation and probably improved its safety.[10–13] Total operative time is about 4 hours. However sometimes it may not be possible, or appropriate, to perform the stapled ileoanal procedure. This occurred in four of our patients, two for medical and two for technical reasons at the time of the attempted stapled operation. Therefore surgeons must be adept at both techniques, including the ability to construct either a J or S pouch.

Although there is a concern that the circular EEA stapler crosses four staple lines, this has rarely been associated with an anastomotic leak. Only 1 of our 21 patients who underwent the procedure developed a leak at this anastomosis and this patient was quite ill and malnourished before his operation. There was one other leak higher in the stapled J pouch that seemed to be temporally related to the inadvertent removal of a suction Jackson-Pratt® drain without opening it to atmospheric pressure.

Avoiding a Diverting Ileostomy

The ease and safety of the procedure led us to perform it without a diverting ileostomy when the operation appeared to proceed without difficulty. This obviates the need for a second operation and its morbidity. Ileostomy following the ileoanal procedure can be technically difficult because the ileum is tethered low in the pelvis. This is a problem particularly in obese patients. Furthermore takedown of the ileostomy also may be quite challenging because the distal nonfunctional ileal lumen may be very small. Several of our patients developed complications after ileostomy closure (Table 2). Complications are noted in several other reports,[14,34–38] following ileostomy closure, with about a 10% rate of ileostomy anastomotic leakage (Table 3). Peritonitis developed in 6.4% of patients from the Mayo Clinic after ileostomy closure, which required re-exploration in all patients and re-establishment of the ileostomy in some.[34] The Lahey Clinic had a 37% rate of ileostomy complications, with 22% requiring surgical correction.[14] We managed our four ileostomy leaks with percutaneous drainage and parenteral nutrition.

It is possible that ileostomy construction and its sub-

TABLE 3. *Ileostomy Complications Collected Series*

Series	No. (%)	Complication
Mayo Clinic[34]	6	Ileostomy leak
Lahey Clinic[14]	37	Complications
	22	Operative correction
Vancouver[36]	27	Complications
	10	Ileostomy leak (1 death)
Finland[38]	52	Complications
	10	Ileostomy leak
Richmond	12	Operative correction
	8	Ileostomy leak

sequent closure may be related in part to the high incidence of small bowel obstruction noted following the ileoanal pouch procedure. Seventeen per cent of ileoanal patients from the Mayo Clinic developed a small bowel obstruction, of whom 7.5% required surgical intervention.[39] We also had several patients with small bowel obstruction in our previous series of patients, although none of the current stapled group have developed this complication to date. While the follow-up is perhaps too short, several patients who had undergone a temporary diverting ileostomy had already experienced episodes of small bowel obstruction during a similar time period.

Several studies evaluated performing the ileoanal operation without an ileostomy. Thow[40] was one of the first to do this. In 1986 a report from the Mayo Clinic described nine patients of 200 who underwent the procedure without an ileostomy, of whom eight had good results.[41] One patient developed jejunal volvulus and perforation after discharge and required pouch excision. They recommended that the operation could be performed in carefully selected patients. Others have had catastrophic results when an ileostomy was avoided.[35] In a study by Everett and Pollard,[37] 29 of 64 patients had a hand-sewn W reservoir ileoanal anastomosis without a diverting ileostomy and had a lower incidence of complications and total hospital stay than did those with a stoma. Five of the 35 patients who had an ileostomy developed complications directly attributable to the stoma. They concluded that, in experienced hands, there can be a considerable benefit in reduction of operative procedures and hospital stay when the ileostomy is avoided. A recent series from Finland, using a stapled J pouch but hand-sewn ileoanal anastomosis without a protective ileostomy, had one patient of 25 who developed an anastomotic leak requiring subsequent construction of a diverting ileostomy.[38] They had also previously noted a high incidence of complications directly related to the ileostomy closure. In one series with a hand-sewn anastomosis without a pouch or ileostomy constructed at the *levator ani* muscle, 4 of 32 patients developed an anastomotic leak.[27]

The only series of stapled ileoanal procedures published to date without a covering ileostomy was that of Kmiot and Keighley.[12] Of 16 patients so treated, three patients receiving steroids had serious postoperative morbidity: one patient developed peritonitis and gram-negative bacteremic shock but no leakage was found at the time of laparotomy 7 days after the ileoanal procedure. A second patient developed a leak at the transected ileum but not at the ileoanal anastomosis. The third patient developed an intussusception of the afferent limb resulting in infarction of the pouch necessitating excision 5 days after the original operation. The authors recommended performing the stapled ileoanal operation without a covering ileostomy only in patients who are not receiving steroids.

Of our 19 patients who underwent the stapled ileoanal operation without a diverting ileostomy, 13 were taking prednisone, 8 underwent the procedure semi-urgently for uncontrollable bleeding, and 3 had significant hypoalbuminemia. Three of these 19 patients developed complications, of whom only one had been taking steroids. This patient also had uncontrollable bleeding and was hypoalbuminemic before the ileoanal procedure; he developed the only leak at the ileoanal anastomosis. In a recent report, subtotal colectomy with an ileostomy and preservation of the rectum as a Hartmann procedure was recommended for the emergent management of severe colonic bleeding in ulcerative colitis.[42] Our data suggest that this degree of conservatism is unnecessary.

The risk:benefit ratio of performing the operation without a diverting ileostomy is yet to be determined. Avoidance of a second operation with its complications may not only significantly reduce hospital costs but also may permit earlier return of the patient to a functional role in society. On the other hand, major morbidity from an undiverted anastomotic leak is a cause for genuine concern and may require three or more operations to control the septic process and restore function. Diversion probably should still be considered for a severely malnourished patient taking high-dose steroids, although a diverting ileostomy was successfully omitted in two such patients in our series. One other disadvantage from avoidance of the ileostomy is that these patients will not experience its inconvenience and thus will be unable to compare it to having frequent stools with the ileoanal procedure.

Stool Frequency

Stool frequency in the stapled J pouch ileoanal patients was similar to our patients who underwent a sutured J pouch ileoanal anastomosis at the dentate line. Excessive stool frequency persists as one of the major problems of the ileoanal procedure. Although some of our patients only have three stools in a 24-hour period with none during the night, some have as many as 15 stools per 24 hours with several during the night, interfering with their sleep. Two patients in the hand-sewn group insisted that their pouch be removed with construction of a permanent ileostomy. In two series, the triplicated S pouch was noted to have a lower stool frequency than a J pouch.[43,44] However this has not been seen in our experience or by other investigators.[45] Harms et al.[46] suggested that a W pouch would have an even greater compliance and lower stool frequency than the S pouch. However in a recent study they did not note any significant differences from an S pouch.[47] Although Harms et al.[47] did not compare the W pouch to a J pouch, no difference in stool frequency or continence were noted by Kmiot et al.[48] between these pouches. Neither the S nor W pouches can be constructed with a surgical stapler and they may also be difficult to anastomose to the anus with the Premium CEEA® stapler.

Thow[40] proposed an antiperistaltic J pouch to decrease stool frequency. We used a similar pouch in 19 patients and found that it significantly reduced stool frequency when compared to a standard J pouch. However several of these patients required insertion of a silastic catheter to evacuate and two patients developed life-threatening complications as a result of their functional obstruction. This led us to abandon the reversed J pouch procedure.

Conclusions

This study supports a stapled, supralevator ileoanal J pouch anastomosis for ulcerative colitis and, possibly, familial polyposis. The operation is easier and appears to be safer to perform than the standard handsewn ileoanal anastomosis. In most circumstances it may be performed without a diverting ileostomy. These patients have significantly better continence, especially at night, than those who have had a mucosal proctectomy and anastomosis to the dentate line. However surgeons who perform this procedure must still be adept at the standard mucosectomy and ileoanal anastomosis technique because sometimes this may be required. Follow-up anoscopic evaluation of the residual anal mucosa will be important but may be difficult to achieve in asymptomatic patients. A randomized, prospective trial will be required before the benefit regarding stool control and overall reduction in complications, duration of hospitalization, and costs strongly suggested by this study and others can be proved. A much longer time will be required before we can be certain that the procedure will not be associated with an unacceptable incidence of subsequent adenocarcinomas.

Acknowledgments

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DISCUSSIONS

DR. JOSEF FISCHER (Cincinnati, Ohio): I do not know of any other group that has experience with the various types of pouches and has analyzed them as carefully as this manuscript.

I would like to make several comments about three different areas that Dr. Sugerman has detailed and then to ask a question.

We emphatically support the retention of the transitional zone. And we continue to believe, and it appears that the data are gradually being accepted, that this is directly related to the preservation of nighttime continence.

It is interesting that the only patient in Dr. Sugerman's more recent series who must wear a pad is the patient in whom the dissection is down to the dentate line. In our early experience with Dr. Lester Martin, when we intentionally dissected down to the dentate line, we had a great deal more difficulty with continence than we do now.

If you look at the incidence of wearing a pad, I am not sure it is all related to the transitional zone. Our incidence of wearing a pad in a group of patients, which now numbers about 200, and we are part of the way through reviewing them with questionnaires and interviews and things like that, is about 7% in those patients without pouchitis.

We have a 6% incidence of pouchitis and we have a 7% incidence of patients without pouchitis who wear a pad, which is about the same as in this study.

Does the concern about leaving the transitional zone involve the kind of epithelium? Is it rectal epithelium or is it a different kind of epithelium? Our experience with many polyposis patients is not to have the regrowth of polyps, and I would wonder whether those patients are really transitioning into Gardner's syndrome, of whom we have seen a fair number with small bowel polyps and also gastric polyps.

I suspect that the length of rectal mucosa that we leave is about the same as Dr. Sugerman. We do not measure, but the distance between the dentate line and the top of the columns, as we estimate it, is about 1.5 cm.

In the early part of the series, when we intentionally left 1 cm additional above where we thought the transitional zone ended, as does Dr. Sugerman, we had trouble with recurrent rectal disease. And 6 of the 12 patients in whom we intentionally left a good length of rectal mucosa have had difficulty, requiring continuous steroids, suppositories, and systemic steroids (one patient), so I do not think that is a very good idea.

The type of pouch is perhaps less important than the length of the sleeve of the exit, which, of course, is not an issue with the J-pouch because you anastomose the J pouch directly to the anus. We continue, because Cincinnati is a very traditional city, to use one form of operation, which is the S pouch. But the one thing we have done is that we have consistently shortened the length of the exit spout to about 5 mm and to make the pouch smaller. And the pouch is now about 10 cm on a side in the stretched state, the S pouch, which we believe contributes to a lower incidence of pouchitis, because the pouch empties completely.

The third question is that of diversion. If, in fact, it works out that the incidence of complications in the patients who are not diverted is lower than the patients who are diverted, then that would be a useful argument for doing some type of anastomosis and not protecting it.

Surgeons have very selective memories. As I was talking to Dr. Sugerman earlier, I said that I did not recall a patient with a leak following an ileostomy closure, but I probably would have repressed it anyway if I had. But we have had a certain number of complications from the ileostomy itself, including stenosis, a number of patients in whom we have had intestinal obstruction. And I had an occasion to revise an ileostomy at the peritoneal reflection last week in a patient 4 weeks after a diverting ileostomy.

The jury is still out on this. But if, in fact, the protective effect of the ileostomy and the leaks and the abscesses is less than that of the complications from the ileostomy or its closure, this is a very significant contribution.

I have only one question, Harvey, and that relates to the sphincter function if you do not divert these patients and they move their bowels quite early. One of the criteria that I use in closing the ileostomy is the softness of the area around the pouch anastomosis. We wait a little longer than most people, about 4 months. The reason I wait 4 months is because that is the time when, at least to my examination, the area around the anastomosis is quite soft.

How did these patients progress? Do they have difficulty early on in retaining their stools and then gradually improve quickly because of the scarring around it? Or is this something that has not been a problem for you?

DR. JOHN H. PEMBERTON (Rochester, Minnesota): In general the results of this operation have been good. This report today substantiates that observation. Our experience at Mayo with a rather large number of these patients also is good.

The questions posed by this paper are very important. Does the double-staple technique actually improve the functional results? This paper, and several others conclude that it does.

However we have reported in the literature several times that the stool frequency and rate of incontinence was largely similar to the reports you heard today. Our patients have about six stools during the day with one at night. And the rate of daytime and nighttime fecal spotting is less than 25% at 3 years. The incidence of gross incontinence is less than 1% at the same length of time after operation.

Clearly, as Dr. Sugerman states in his manuscript, the only way to determine if function is improved after ileoanal anastomosis will be to conduct a prospective randomized trial.

If such a trial shows that the double-staple technique indeed does improve continence, then the second question must be addressed: what implications are there for patients with retained rectal mucosa.

Dr. Sugerman does, unlike some people in the literature, face this issue squarely. All but one of his patients had residual disease. One might, therefore, make a reasonable case that the operation presented was actually an ileorectostomy and not an ileoanal anastomosis. This, of course, brings up a whole new set of controversies that really go right to the heart of the rationale for doing the ileoanal operation in the first place. I must stress that we do not have to worry about the second question until a trial can determine whether there is really functional improvement.

Regarding diverting ileostomy, it would be great if we could eliminate an ileostomy from this operation. We, however, have covered nearly all of our patients with an ileostomy because a stoma-related complication is bothersome but repairable, while pelvic complications such as pelvic sepsis, and its sequelae are not.

How would you advise us, then, on choosing the right kind of patient for a single-stage procedure? Finally, I worry about incorporating the posterior vaginal wall in stapled low anterior resections. This, of course, is a very low stapled resection. How do you prevent this?

DR. WILLIAM P. J. PEETE (Durham, North Carolina): I want to focus my comments on the one patient Dr. Sugerman had with congenital polyposis. In 1983 Dr. William Waddell and Richard Lowry reported the resolution of polyps in the colon of four patients who had Gardner's disease treated with Sulindac.

In 1989 the expert in this Society, Dr. Elmo Cerise, and Gary Ganzer joined with them to report seven more patients. Now they had seven patients with Gardner's disease, four patients with familial polyposis coli, seven patients who had partial colectomy and ileoproctostomy and four patients who had the polyps treated in an unresected colon. As long as the patients took the Sulindac there was complete resolution of the polyps.

About this time last year I was presented with a patient from West Virginia who had more than 200 polyps identified in his colon by colonoscopy examination, one at the hepatic flexure was carcinoma *in situ*. I thought it appropriate to remove his abdominal colon and carry out an ileo low sigmoidostomy. He was discharged 7 days later on 200 mg of Clinoril a day. A month later he was found to have 27 polyps in his rectum. I have followed him serially for more than 1 year. Most of the polyps disappeared by April.

When I scoped him 2 weeks ago, there were no polyps in his rectal segment and he was having one to two bowel movements a day.

The next patient is different. In 1988 a 52-year-old man had a 7 × 6 × 5 cm villus adenoma removed from his rectum with subsequent low anastomosis. The margins were free. However, in April of this year, I found that he had a 2 × 3 cm recurrent villous adenoma near his suture line and a 9-mm polyp below the splenic flexure.

This slide shows a biopsy done in April of 1990. The patient was told of this work with Clinoril and, facing a possible proctectomy and colostomy, and knowing that he had a benign lesion, at least according to that biopsy, which shows villus adenoma, he agreed to take Clinoril, 200 mg, twice a day.

Two months later you see the possible effect of blocking prostaglanden, diminishing DNA and perhaps tumor growth factors. The tumor at that time was one half the size it had been. I follow him every 2 months.

In November he had a repeat biopsy. He still has tumor but less.

This interesting patient makes one wonder what effect Clinoril may have on other polyps of the colon. His 9-mm polyp near the splenic flexure has not been apparent to me on endoscopy since June. Therefore it is possible and perhaps probable that we have an effective chemical prevention for carcinoma in patients with polyposis coli whether most of the colon has been removed or whether only that portion in the abdomen has been removed, possibly for other polyps.

The main side effects of Clinoril are well known.

Clinoril is moderately expensive. Two patients stopped taking it with polyp growth; then resolution when it was restarted. Even so, in the treatment of patients with polyposis coli, a total colectomy with ileostomy or near-total colectomy with very low anastomosis is probably unnecessary. Work and time will tell. Whatever route of treatment is followed, careful follow-up is essential.

DR. HARVEY SUGERMAN (Closing discussion): With regard to the anal transition zone, I kept pleading with our pathologist to tell me if this was anal transition zone and not actual columnar epithelium, but they refused to cooperate. In all of the specimens they confirmed the fact that this was columnar epithelium.

The length of the tissue between the anastomosis and the dentate line improved with time. So as we became more experienced with the technique, we got closer to the dentate line. But as mentioned, there is a point to which you should not go, and I think you do sacrifice continence and control when you get down to the dentate line.

This is different from the Mayo Clinic data, as most of the published series do describe better fecal control when some residual tissue above the dentate line is retained. And, as I will mention again, a randomized study is mandated to answer the questions prompted by this study.

In terms of the pouch type, we, too, had three 10-cm limbs with our S pouches, but our average spout was about 2 cm. This seemed to stretch sometimes because of tension since in many of these patients with the S pouches it was done because we needed more length. And we get the greatest length with the S pouch.

With regard to the ileostomy, yea or nay, it is two operations and two hospitalizations under the best of circumstances. And, in addition, you have a tradeoff between the complications, and there are complications in all series with the ileostomy itself as well as without the ileostomy.

One of the crucial questions, as already posed, is whether the disastrous complications that could occur if you do the operation without an ileostomy are life threatening or can be picked up early enough that you can save not only the pouch but, most importantly, the patient's life.

So it is important to be aggressive and operate early, with a diverting ileostomy; if a leak occurs if you do this operation without an ileostomy.

With regard to sphincter function without diversion, that is one of the negative aspects of the operation. They seem to go slightly more often at the beginning as when they've had a diverting ileostomy that you close, because at the beginning the stool tends to be more watery and burning. It may be a bit better after they have had an ileostomy, since they have had some time for the ileum to compensate. But the problem is that these patients have not had an ileostomy to know how unpleasant an ileostomy can be. And that, in a way, is a negative aspect. Because when they are going a lot at the beginning, they can not relate this to having had an ileostomy and say 'I'm willing to accept this so that with time it's going to get better.' But in our experience there has not been much difference whether the patients have or have not had an ileostomy in terms of their initial control.

With regard to whether this is an ileorectostomy rather than an ileoanal procedure, I think that is only a matter of semantics. Is this the bottom of the rectum or the top of the anus? I think it is both. And the key issue is that this is not the ileoproctostomies that used to be constructed.

If you look at the published series with regard to the ileorectal anastomoses, they average about a 6% incidence of adenocarcinoma. And this is preserving somewhere between 10 and 15 cm of the rectum for that procedure.

The risk of cancer is projected actuarily to be 15% cumulative in a period of 30 years. So this must be significantly lower in our patients with 1.8 cm residual tissue. It will be there, and it will be a concern.

One of the other issues, therefore, is follow-up, and that is a genuine problem. Follow-up is easy because all you need to do is anuscope the patient. The problem is that many of these patients are feeling so good and are so asymptomatic that they do not want to come back.

I have concerns about the staple procedure for the polyposis patients. I am concerned that we may be leaving some residual tissue that could form polyps, and I think that those patients may be at somewhat greater risk. Again it would be easy to examine them, it would be easy to fulgurate them, it would be easy to excise them. But the question is patient follow-up and the cooperation of your patients.

The other issue is rectal bleeding. You may have bleeding because of residual disease; you may have bleeding because of pouchitis; or you could have bleeding because of the development of a carcinoma. And it will take many years before we know what that potential risk really is.

With regard to the risk of a rectovaginal fistula, we have not had a single rectovaginal fistula in this group. It is important in doing the operation that you dissect the rectum all the way down to the levator sling, circumferentially so that you are not getting the vagina when you come in with the pin on the EEA instrument.

With regard, finally, to the polyposis issue of Clinoril or Sulindac, to use the generic name, I have not seen any data on that. I find the concept interesting.

There are other complications with Sulindac. It induces severe pancreatitis. And in fact, the father-in-law of our Chief of Urology developed fulminant pancreatitis secondary to Sulindac. The appropriate procedure is to do a subtotal colectomy, proctectomy, and ileoanal procedure in one way or another for these patients, and then you do not have to worry about their polyposis problem.

Finally we must have a randomized prospective trial to evaluate stool control function with either leaving the residual mucosa behind or using it as a stapled *versus* the hand-sewn technique at the dentate line. And, second, there is a need for a randomized prospective trial to do the operation with and without an ileostomy. It's safe to do it with the staple technique and without an ileostomy. As you saw from our data, our complications were rare, but the one major complication we had was in a severely malnourished patient.

We had 13 patients on Prednisone, 8 for fulminant colitis, 3 of whom were severely malnourished. One of those three is the one who developed the leak. If a patient has a very low serum albumin, it is appropriate to be more conservative.

The MAGPI Hypospadias Repair in 1111 Patients

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The meatal advancement and glanduloplasty (MAGPI) procedure was first described in 1981 for the repair of distal hypospadias. In the past decade, our experience has grown to more than 1000 procedures. An excellent surgical result requires careful case selection, avoiding cases with thin or rigid ventral parameatal skin or a meatus too proximal or too wide. The glans wrap to support the advanced ventral urethral wall requires a solid tissue approximation in two layers to prevent a retrusive meatus. Meatal stenosis can be avoided by assuring an adequate dorsal Heineke-Mikulicz tissue rearrangement and making an incision from within the urethral meatus well distally into the urethral groove. The MAGPI procedure routinely is performed on an outpatient basis without any urinary diversion. Our experience in 1111 cases during 12 years has required a second procedure in 1.2% of cases. The overall success rate with the MAGPI procedure suggests that it should continue to be used in the repair of distal hypospadias.

IN 1981 WE[1] DESCRIBED a hypospadias technique for advancement of the meatus and reconfiguration of the glans for the most common manifestation of this anomaly. Since its introduction the meatal advancement and glanduloplasty (MAGPI) procedure has withstood the test of time, has become internationally accepted, and is the most common hypospadias technique used today.

Hypospadias occurs in 1 of 300 male births with the meatus position distal in 65%, in the middle of the shaft in 15%, and in the penoscrotal or scrotal position (posterior) in 20%. In those with the anterior classification, the dystopic meatus is located on the inferior glans 15% of the time, in the coronal groove 50%, and subcoronal 30%, and the megameatus intact prepuce (MIP variant) in 5% of cases. Perhaps 50% or more of these anterior variants will be amenable to the MAGPI. Approximately one third of all cases of hypospadias are suited for this single repair. While we have continued to be satisfied with this operation, others have reported excessive meatal retraction and meatal stenosis.[2-6] Our purpose in this paper is to review our results and describe the modifications of the procedure we have added since its original description that will help others avoid the reported complications.

Results

Records of patients who have had the MAGPI procedure performed at The Children's Hospital of Philadelphia were reviewed for the period July 1987 to May 1990 (282 cases). The complications were itemized as to fistula, meatal retraction, presence of chordee, meatal stenosis, or cosmetic skin irregularity. Two cases required secondary surgery, one with a fistula and one with persisting chordee, for a 0.8% rate of reoperation. Previous reviews that we reported comprised the cumulative results of 1111 cases. From 1978 to 1981, 207 cases were reported[1]; from 1981 to 1985, 510 cases[7]; from 1985 to 1987, 128 cases[8]; and from 1987 to 1990, the current 266 cases reviewed herein. Thus an average of 85 cases per year were managed. The complications included 5 fistulas (0.45%), 7 meatal retractions (0.6%), 1 residual chordee (0.09%), and no meatal stenoses. The incidence of complications requiring secondary surgery was 1.2% for the entire group. For the last 5 years it was 1% (4 of 394 cases) (Table 1).

The average follow-up was 2.3 months, with a 2-week to 2-year range. No follow-up was obtained in 16 of the 282 cases (6%). We think an average follow-up of 2.3 months is adequate to assess the outcome of healing of this type of hypospadias repair. It would be more complete to have long-range assessment of these patients; however we think that it is psychologically inappropriate to have a child come back for evaluation of a congenital anomaly

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TABLE 1. *Cumulative Results of MAGPI Procedure*

Dates	Number	Fistula	Regression	Stenosis	Chordee	2nd Surgery (%)
1978–1981	207	1	4	0	0	2.4
1981–1985	510	2	2	0	0	0.8
1985–1987	128	1	1	0	0	1.5
1987–1900	266	1	0	0	1	0.8
Total	1111	5	7	0	1	1.2

that, in essence, has been repaired completely before his knowledge of the anomaly. Because most of these anomalies are repaired when the child is 6 months to 1 year old, the child does not remember the operative experience. The parents are instructed to subtly observe the child's urinary stream periodically throughout childhood to make sure there is no splaying, diminished force, deflection, or cosmetic skin irregularity. The parents are encouraged to return for a visit whenever they feel the need for re-evaluation. This rarely occurs because the repair typically matures nicely with the child.

Selection of Cases and Technique

The technique for the MAGPI procedure has been modified considerably since it was first described in 1981. Textbook and atlas diagrams have been modified through the years, but it is still difficult to depict adequately the meatal enlargement and advancement and the three-dimensional glanular rearrangement that is required for the excellent cosmetic result that can be achieved.

In selecting a case for the MAGPI repair, the nature of the meatus and the parameatal skin is of paramount importance in achieving a successful glans reconfiguration. The parameatal skin should be thick and pliable, permitting it to be lifted easily off the underlying urethra. This is essential to permit the ventral parameatal skin to be advanced distally. The glans configuration must permit it to wrap around this advanced ventral urethral wall. If the parameatal skin is thin or nonpliable, then the MAGPI procedure is inappropriate.[9] An onlay island flap[10,11] often is more appropriate.

The size of the meatus also is an important consideration. Usually the meatus is small and after the ventral wall has been advanced distally, it is not difficult to dissect laterally to expose the glans for the placement of sutures solidly into glans tissue (Fig. 1g) to reconfigure it from its typically flat configuration into a more normal conical shape. The healing of glans to glans maintains the ventral support for the advanced meatus and thus prevents later falling back of the ventral meatal wall, a retrusive meatus.

If the meatus is large, as is usually seen in the MIP variant of hypospadias,[12] then the glans cannot be exposed for the placement of the glansplasty sutures, and either a pyramid[12] or Mathieu[17] procedure with a glansplasty involving formal mobilization of glans wings will result in a more satisfactory long-term glans reconfiguration.

In cases of distal hypospadias, it is rare to see chordee due to more than a ventral skin or subcutaneous tissue abnormality. The flattened glans so frequently seen in these cases appears to indicate that once the shaft skin has been dropped back, an artificial erection will reveal straight corporal bodies.

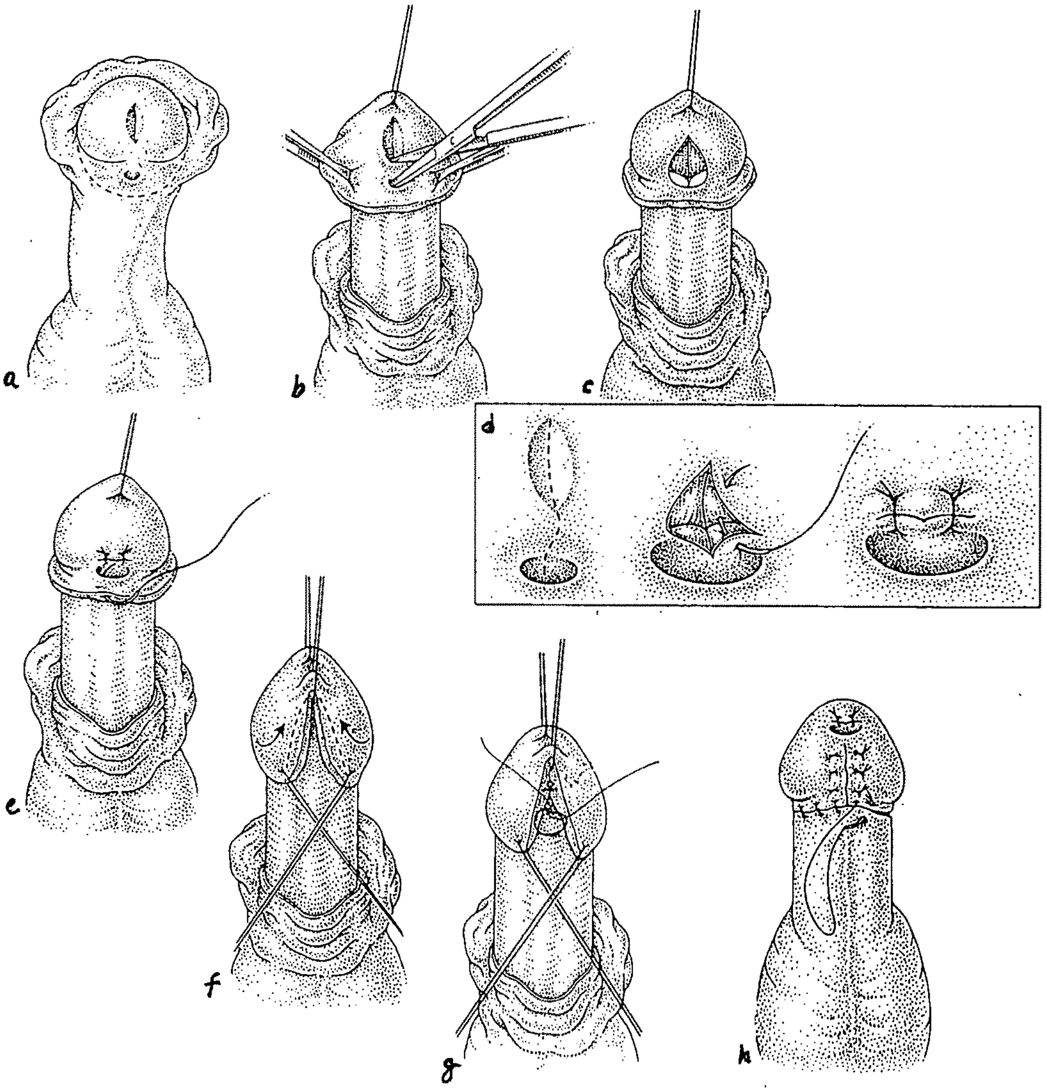
Cases ideal for the MAGPI procedure usually have a meatus positioned at the coronal margin or subcoronally. There is commonly a lip of tissue distal to the meatus that deflects the urinary stream ventrally to a variable degree. The glanular groove varies in its depth and may require deepening with the initial Heineke-Mikulicz maneuver that advances and flattens the dorsal urethral wall. This step corrects the ventral deflection of the urinary stream. Often there is an accessory dorsal periurethral duct located in the glanular groove distal to the meatus, but this does not interfere with the repair.

Technique

After a holding stitch of 5-0 prolene is placed in the glans for traction, a 1:100,000 concentration of epinephrine in 1% xylocaine is injected in the subcoronal area and glans groove. A circumferential incision is made around the corona proximal to the meatus. The exact placement of this circumferential incision is not important at this stage because excess skin will be trimmed as the glanuloplasty develops. Others[2,13,14] have indicated the importance of the initial incision in the construction of the future glanular configuration; however we think it is not necessary to configure a definite skin incision unless the Firlit skirt or mucosal collar is used.[14]

The penile skin is mobilized as a sleeve back to the penoscrotal junction and thus results in freeing of the tethering fibers of the subdartos fascia, particularly on the ventrum. This is the most probable cause for the ventral tilt of the glans frequently seen in these cases. The straightness of the penis is checked with an artificial erection. If curvature is present, this is usually caused by corporal disproportion and not chordee involving the dorsal urethra. Correction is carried out easily using dorsal plicating sutures.[15]

The meatal advancement of the dorsal urethral wall is accomplished by a Heineke-Mikulicz vertical incision and horizontal closure. More commonly now wedge removal of a segment of glanular tissue distal to the meatus, which includes the dorsal meatal wall, is performed. This horizontal closure flattens out the glanular bridge and permits the dorsal urethra to be advanced out onto the glans tissue to the apex of the glanular groove where it is sutured with interrupted 7-0 vicryl. This flattens the deflecting ridge of glans and permits the stream to be directed forward.



FIGS. 1a–h. MAGPI (Duckett series) (a) A circumferential incision is made proximal to the corona and proximal to the meatus. (b) The skin is dissected down to the penoscrotal junction freeing up all tethering dartos bands, assuring a straight erection with an artificial injection of saline. (c and d) Meatoplasty: A vertical incision is made in the transverse web between the meatus and distal glans groove, extended proximally into the dorsal meatal edge. This creates a diamondlike defect that is closed transversely, advancing the dorsal meatal lip into the glans groove. A transverse closure is made (Heineke–Mikulicz). (e–h) Glanuloplasty: A holding stitch is placed on the ventral meatal edge and elevated forward (e), thus configuring the glans in a more conical shape (f). Excess skin on the ventrum is excised and the glans edges are approximated with a deep layer of absorbable suture and a superficial chromic layer (g). (h) Skin cover.

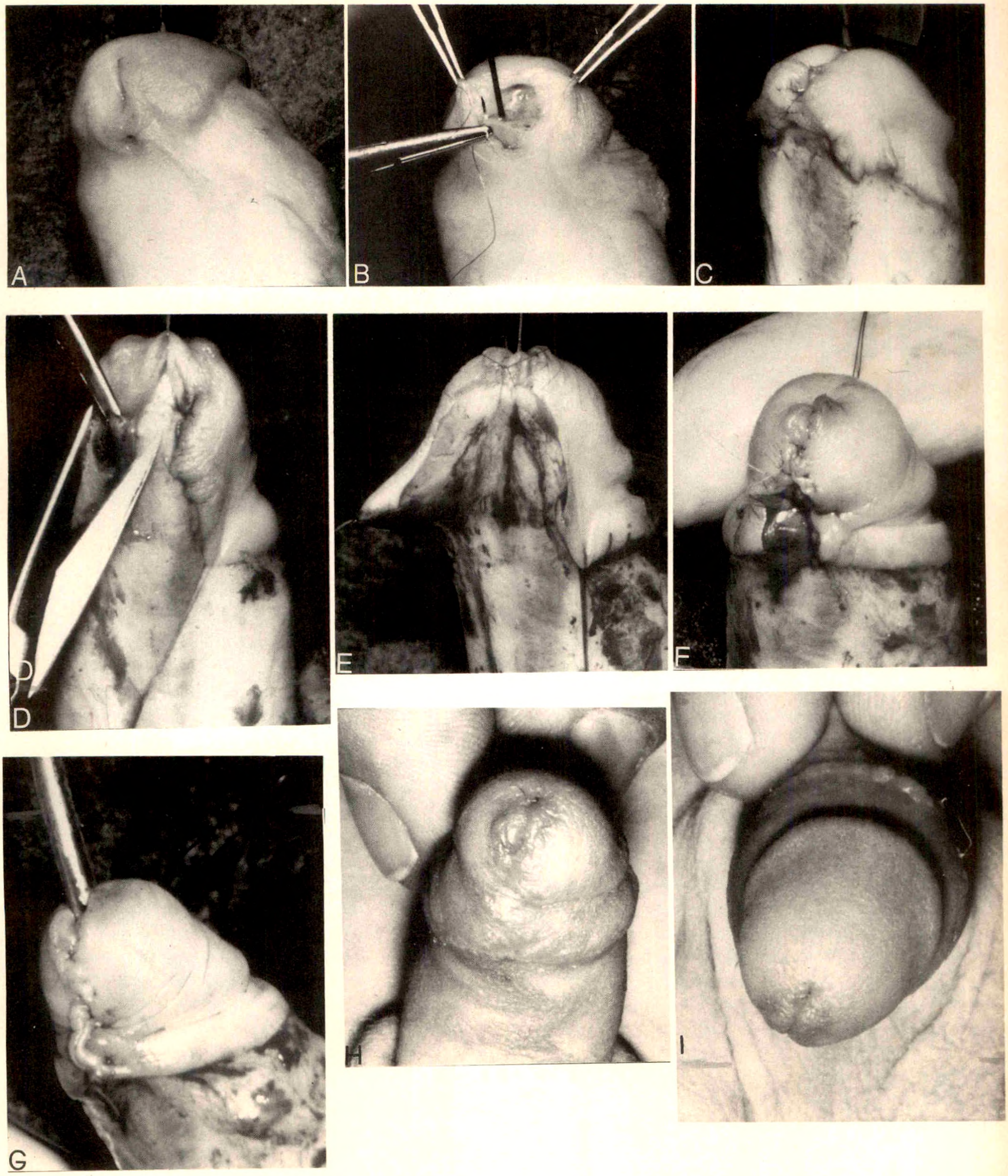
The glanuloplasty is made by reconfiguring the flattened glans into a conical shape. By rotating the lateral wings around to the midline proximal to the meatus, a proper conical glans shape can be recreated. There will be skin adjacent to the glanular edges that must be excised in a precise angle to reapproximate the glanular wings together in the midline on the ventrum (Fig. 1). The deep glanular tissue is brought together with interrupted 6-0 vicryl or PDS interrupted sutures and the superficial epithelial edges are run with 7-0 chromic suture. In this manner mesenchymal glans tissue heals to glans tissue between the epithelial layers of the urethra and the outer epithelium of the glans, and this prevents meatal retraction. This rotation of the glans wings reconfigures a nearly normal glanular appearance. A bougie-a-boule is used to calibrate the meatus and ensure that the glanuloplasty has not compromised the lumen of the distal glanular urethra.

While a sleeve reapproximation of the penile skin usually is sufficient for skin cover, ventral transposition of the preputial skin may be necessary to replace a skin deficiency on the ventrum. Fine 7-0 chromic is used for the skin closure to help avoid the development of later suture sinuses.

No stents or catheters are required for diversion. These procedures are done in the day surgical unit. A vaseline gauze dressing that is similar to a circumcision dressing will cover the incision for 24 to 48 hours and is removed by the parents at home.

Discussion

For many years techniques were not available to reconstruct reliably the urethra out to the tip of the glans in patients with a distally placed meatus. Because there was minimal functional impairment, surgeons were reluctant to subject a patient to complications that might be more severe than the untreated anomaly.[16] Techniques available to correct distal hypospadias, Mathieu,[17] Mustarde,[18] and Devine-Horton flip-flap,[19] require the construction of a neourethra. The MAGPI procedure allows



FIGS. 2A–I. MAGPI (operative series). (A) Typical meatal location with distal bridge of tissue to be removed in a wedge. (B) Glanular groove opened to apex and into dorsal meatus. Note generous meatal mucosa; probe in paraurethral duct. (C) Straight erection after skin takedown; slitlike meatus at apex. (D) Ventral view with holding stitch in ventral meatal edge; excess skin trimmed up to epithelium of glans. (E) Suture is approximating mesenchymal thick glanular tissue as deep layer with holding sutures on glans wings. (F) Closure of glans epithelium with fine chromic. (G) Glanuloplasty complete; catheter in meatus at apex. (H) One month postoperative result: conical glans; slitlike meatus.

the surgeon to avoid a urethroplasty and provides a reliable, reproducible procedure for reconfiguring the glans and meatus without the use of catheters and with a very low morbidity rate.

Diagraming the technique for teaching the method has been difficult. In the past 10 years,[7–9,15] modifications have been made that bring glanular tissue together in a more solid ventral closure that avoids meatal regression. An additional layer approximating deep glans tissue has been added that replaces the vertical mattress stitches described in the original diagram[1] (Figs. 2f and g). The glans mesenchyme is now approximated deeply, with an epithelial layer closure superficially. This is a more secure closure to avoid the ventral glans separation that leads to meatal regression. Usually the glanular reconfiguration produces a nearly normal-looking glans with an unnoticeable ventral glans scar.

Fortunately meatal stenosis has never been a problem with this reconstruction, although it is reported by others. When the dorsal incision is made vertically and closed transversely, this opens up the meatus in a wide configuration. While many of these anomalies have a significant meatal stenosis to begin with, the meatoplasty in a Heineke-Mikulicz fashion suffices to widen this in all cases when the incision is made well into the stenotic meatus.

The ventral meatal edge is elevated forward and the glans wings are rotated medially, reapproximating the normal conical glans shape. The meatal advancement is maintained as a result of glanular rotation and secure healing to glans. The ventral meatal edge is fixed to the glanular tissue with interrupted chromic sutures to keep it from retracting beneath the glansplasty.

Some modifications of the technique have been used in specific cases. For instance the ridge of tissue in the glanular groove may be quite thick so that a transverse wedge must be removed to advance the dorsal urethra further into the glans. At other times the glanular groove may be quite wide with a prominent lip on each side. This redundancy may leave a fold of the meatal lip as a lateral 'dog ear.' A transverse excision of these is needed to create a vertical neomeatus. The meatus may be extended even further toward the apex of the glans in some cases with a wide groove by denuding the epithelial layer ventrally and stitching these edges together.

Inappropriate application of the MAGPI technique to unsuitable cases causes most of the poor results reported by others.[3,6] The ventral distal urethra must be mobile to be advanced into the glans. The MIP variant (megameatus with an intact prepuce)[12] is definitely not a proper selection, nor is the wide, deep meatal groove with a subcoronal meatus.

Modifications of the MAGPI that have distinct indications have been developed by others. Arap[4] proposed a method of urethral extension for those cases with a more proximal meatus. The ventral meatal edge is brought forward with two holding stitches 7 to 10 mm apart in an 'M' configuration. The middle 'V' of the 'M' is closed, forming a urethral extension that is buried beneath the glanular approximation. A dorsal meatal advancement is not beneficial in this setting.[5] A glans approximation procedure[20] was published recently, but it does not relate to cases amenable to a MAGPI.

Others have reported their results with the MAGPI. Livne et al.[21] had excellent results in 66 cases with no meatal stenosis or retraction, with only three cases having minor cosmetic deficiencies. MacMillan et al.[22] studied 44 MAGPI results with photographs of their streams and uroflows. All but one case had an excellent cosmetic result (one small meatal flap was later considered acceptable with no surgery). Photography of the streams demonstrated a satisfactory if not entirely normal pattern and flow rates were normal. They stated 'Until recently, the price of perfection in the management of anterior hypospadias was significantly high. However, with the advent of the MAGPI repair, which virtually guarantees perfect cosmetic results and fully preserves micturitional function, all boys with distal hypospadias should be offered early surgical correction.'[22]

Others report unacceptable results. Ozen and Whitaker[13] had a 6% rate of meatal retraction in 67 patients and only 91% excellent results. Issa and Gearhart[6] described eight cases with meatal retraction, five attributed to technical failure and three to poor case selection. The recent report of Hastie et al.[3] described a significant meatal retraction problem but none back to the position of the original meatus, and the direction of the urinary stream was not affected.

After 10 years of experience, the primary criticisms of the MAGPI procedure are meatal regression and meatal stenosis. Our attention now is focused on teaching surgeons to avoid these problems. First the meatoplasty must extend the dorsal incision into the meatus to increase caliber. Second the glans wings must be brought together ventrally and fixed snugly to assure solid healing to avoid meatal regression. Our results have confirmed that when properly selected and executed, the MAGPI technique for hypospadias is very successful with a low morbidity rate and great parental satisfaction.

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DISCUSSIONS

DR. MAURICE JURKIEWICZ (Atlanta, Georgia): This was a splendid presentation of a straightforward, deceptively simple procedure described originally by the author in 1981, as he indicated to you, for distal hypospadias repair.

Coronal and subcoronal hypospadias, as he indicated, is the most common variant of this anomaly, which is among the most common of the somatic malformations occurring, as he indicated, in as few as 1 in 300 live births. Before the description of this operation, there was no good, reliable procedure to correct the extreme deformation, the appearance of the penis, and the accompanying ventrocurvature simultaneously. All previous procedures involved construction of a neourethra from the existing penile skin. Furthermore, until the Horton-Devine turnover flap procedure, reconstruction involved two stages with attendant complications.

Thus, unless there was a significant degree of ventrocurvature, the coronal hypospadias, in general, was left uncorrected. And so it was with training and my practice.

Before John Duckett, the late Lewis T. Byars of St. Louis, a member of this Association, a Regent of the College, and the man who was my principal teacher of reconstructive surgery and was, arguably, the best hypospadias surgeon around.

He devised a two-stage procedure adaptable to most hypospadias repairs, and in his hands it was remarkably free from complications. For example, when I completed my residency, he had a consecutive series of about 135 repairs without a single fistula, which was an unmatched record.

His operation, properly done, actually brought the meatus very close but not quite to the tip. In his procedure the glandular epithelium was replaced in the first stage by preputial skin. He emphasized this glandular reconfiguration, just as Dr. Duckett has, to give a normal appearance. However, because skin was used to construct a neourethra, stream deformation was a problem.

In the manuscript, to facilitate the dissection, Lidocaine and Epinephrine are injected into the penis. This operation is done at a very early age now, 6 months to 12 months. Dr. Duckett uses 1% Lidocaine with 1 to 100,000 Epinephrine, and I take it you have had no problems with it.

I have used 0.25% with 1 to 400,000 Epinephrine, which gives you the same amount of hemostasis and obviates any toxic problems or flap problems.

These are done, as I understand it, as day surgery procedures, and I wonder if you would supply some information about the instructions to parents, how many of these patients have had to come back because of bleeding, or other problems.

To my knowledge, this is the first time any paper on congenital anomalies of the genitalia has ever been given before this Association.

DR. PAT MOYNIHAN (New Orleans, Louisiana): As a pediatric surgeon, I really do not do hypospadias repairs, but I follow with interest many of the patients that I see and refer to my urologic colleagues. It seems that the major complication outside of Dr. Duckett's group is meatal regression, and I would like your thoughts on the primary cause of meatal regression.

When you have this complication, how soon do you do a second repair?

The other thing I'm interested in, because we do so many outpatient surgeries at the present time, is what percentage of your patients do you do as outpatients, and are they a highly selective group?

DR. JAMES O'NEILL (Philadelphia, Pennsylvania): I enjoyed the opportunity to read this manuscript. This is a complicated paper about a complicated subject, notwithstanding Dr. Jurkiewicz's remarks about it being deceptively simple.

I have been an avid pediatric urology watcher and perhaps a Duckett watcher for the last 9.5 years and have been convinced about the validity of this procedure. Let me summarize by saying that all previous procedures that I have been aware of have involved construction of a neourethra, that is, a urethroplasty.

What Dr. Duckett and his colleagues did in 1978 when they initiated the procedure was to simplify repair by eliminating the need for urethroplasty while at the same time following the principle that a two-layer closure of good tissue is necessary for success.

What he has learned, as have his colleagues over time, is that not all patients with these anterior forms of hypospadias are amenable to the original MAGPI or, as the Europeans call it, the Duckett operation, so it has been modified over time.

He has also learned which cases to avoid when applying the MAGPI, and he might tell us a bit about that. For these, he devised the island flap on-lay procedure that he showed you in 1985.

The message is that the surgeon who undertakes hypospadias repairs must be experienced in judgment and capable of performing a variety of operative procedures. With proper patient selection, Dr. Duckett and his colleagues have been able to perform a huge number of repairs with a current reoperation rate of less than 1%, which is two to three times better than any other operation has ever been and, particularly, the more recently reported ones from France and Canada.

Furthermore, as you have heard, these procedures are now done on a day-surgery basis and even more impressively without stents or catheter diversion, which are necessary if a urethroplasty is done.

Overall it is a relatively simple approach that results in penile straightening, appropriate urethral and meatal advancement, and normal anatomic appearance with a minimal complication rate in terms of the main problems, meatal retraction, and meatal stenosis.

Interestingly, despite Dr. Duckett's honesty about two groups that have had some problems, most others have been able to reproduce or at least approach Dr. Duckett's results, which further verifies the validity of it.

My only caution and, perhaps, question to Dr. Duckett has to do with the follow-up. In the manuscript and on one of your slides, you indicate an average 2.3-month follow-up and indicate the potential psychologic undesirability of long-term examinations. However a 1-year follow-up will only make most of these children 2 years old, and I doubt that it would bother them very much to be examined.

A 1-year follow-up might be a better time to see the full effect of scar relaxation and perhaps better verify the absence of meatal retraction.

The latter comment notwithstanding, Dr. Duckett has reported the best available results with repair of the most common form of hypospadias. It is no surprise that this has become the international standard by which everything else is judged in this field.

DR. JUDSON RANDOLPH (Washington, D.C.): I rise to give a bit of historical perspective to add to Dr. Jurkiewicz's remarks. When I was trying to learn to be a pediatric surgeon 35 years ago, this particular form of hypospadias was largely recommended for conservative treatment. There was such a history of stricture, of leaks, of complicated deformities after surgery that most surgeons who dealt with this problem said, 'The urethra is near the glans and the patient can stand to void, and we believe he can impregnate a female, and it's better left alone.' And except for Dr. Beyers and Dr. McCollum in Boston and a few other such persons, the procedure for this group of patients, which was more than one half the patients, was not to operate.

I started to ask how many in this audience are grandfathers, and I look around and I see that many of you qualify. So grandfathers and fathers know that when a baby is born, as soon as you ascertain if his brain is all right, you want to know if his artillery is all right. So this has become a very impressive, important thing to find out about. And then, as we heard Dr. Duckett easily use the phrase the Heineke-Mikulitz principle, we realize that he certainly demonstrates a bias of mind. He was a fully trained general surgeon before he became a urologist and then a pediatric urologist, so that the principles that he has used come easily to his hand and to his mind.

I know that Dr. DeBakey, our president, Dr. Gross, my old teacher, and also Dr. Duckett solved and have solved surgical problems, as many of you in this audience, by looking at the problem, bringing the simplest surgical principles to bear to make for a new, clean approach. And I think that is what Dr. Duckett has presented to us this morning.

Finally it is true that this operation is being done in the operating rooms across this land and around the world. It is very reproducible, attesting further to the clean simplicity and effectiveness of this procedure.

And I might also say that Dr. Duckett's father, Dr. Duckett of Dallas, a general surgeon who was for many years a member of this Association and is known to some of you here, looks down with pride on this accomplishment.

DR. JOHN W. DUCKETT (Closing discussion): Aside from being a little choked up after the last comment—Dr. Jurkiewicz, I appreciate your historical perspective. To answer your questions, we picked the 1 to a 100,000 dose because it's effective and we don't have to wait quite as long as with 1 to 400,000. We have had no untoward complications with that concentration, and our anesthesiologists tell us we may use plenty of it without side effects.

We do these as outpatients, and that saves a lot of time and effort. Because it is a simple procedure without a urethroplasty, there is no urinary diversion. Even in our more complex surgeries with the island flaps, we use a little silastic splint that is spaghetti size and very flexible. We sew that to the glans and let the patients go home on the same day.

So none of our hypospadias cases are done as in-hospital procedures anymore. We send them home with specific instructions and very few need to return with complications.

Dr. Moynihan I appreciate your comments. The meatal regression is the key problem, and I think there are two factors related. One is the misselection of cases. Too many times this typical case that I showed you today is not present. The meatus is wide, is not flexible, and not moveable. There is just nothing you can do to move that type of meatus forward. A MAGDI will lead to meatal regression.

The second part, and the one I emphasized today, is getting that two-layer glans closure so that it is firmly approximated and avoids the breakdown. We had initially shown a vertical mattress suture that held the two layers together, and we have replaced that with two suture layers rather than the vertical mattress.

Dr. O'Neill you zeroed in on the major criticism of our work, and that is the inappropriate length of follow-up. We have rationalized that since this is done in a child with no recall of the surgery having them return at age 2 to 4 years focuses on a problem with their penises. We were pretty convinced over this 13-year experience that we really did not have that many problems after the 2- to 3-month evaluation. Remember that is an average; so most of the evaluations were at 6 months.

And finally, Dr. Randolph, I appreciate the perspective of your career in pediatric surgery and your recognition of the complexity of this anomaly's repair. I particularly appreciate your comments about my father.

Choledocholithiasis

Endoscopic Sphincterotomy or Common Bile Duct Exploration

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A prospective randomized trial was conducted of preoperative endoscopic sphincterotomy and surgery (ES&S) or surgery alone (SA) in 52 patients with cholecystolithiasis and choledocholithiasis that were candidates for elective surgery. After ES&S 65% of patients were stone free. Eighty-eight per cent of patients with SA were stone free after surgery ($p < 0.05$). Three patients in each group had residual stones at the completion of the operation. Five of these six had more than 20 common bile duct (CBD) stones. There was one episode of major hemorrhage in a patient in each group and no deaths. Costs were essentially equal for the individual patient with a successful ES as compared to SA. Societal costs of a program of preoperative endoscopic retrograde cholangiopancreatography and ES would be higher because of the cost of screening for patients with CBD stones. These results do not support preoperative ES as a technique for clearance of the CBD of stones on the basis of efficacy, morbidity rate, or cost.

CHOLECYSTECTOMY, FIRST PERFORMED by Karl Langenbuch in 1882, has become the standard therapy for symptomatic cholecystolithiasis.[1] Newer options available for treatment of cholecystolithiasis include laparoscopic,[2] lithotriptic,[3] and endoscopic techniques[4] and chemical dissolution.[5] Common bile duct (CBD) stones present or suspected at the time of cholecystectomy traditionally have been treated by choledochotomy, common bile duct exploration (CBDE), stone retrieval, and T-tube placement. The newer techniques mentioned above also can be used in the management of choledocholithiasis.[4,6,7]

This report will concern a prospective randomized study of preoperative endoscopic sphincterotomy (ES) in conjunction with surgery (ES&S) or surgery alone (SA) in patients with chronic cholecystitis with cholecystolithiasis and choledocholithiasis who were candidates for elective surgery. Whether, in such patients, ES is as effective as CBDE in retrieval of CBD stones and what is the relative morbidity of these two approaches have not been established. Costs will be compared.

Methods

Patients admitted to the Los Angeles County—University of Southern California Medical Center with a diagnosis of cholecystolithiasis and possible choledocholithiasis and who were candidates for elective surgery were considered for entry into the study. Cholecystolithiasis was documented by ultrasound in all patients and choledocholithiasis was suspected on the basis of a serum bilirubin level greater than 2 mg/100 mL, previous hyperamylasemia, or ultrasound examination that revealed either a CBD larger than 1 cm in diameter or probable CBD stones, or both. The study was approved by the Institutional Review Board and informed consent was obtained from each participant. All patients underwent endoscopic retrograde cholangiopancreatography (ERCP). Those with CBD stones were assigned randomly to one of two groups, preoperative ES and surgery (ES + S; group 1), or surgery alone (SA; group 2). A computer-generated randomization sequence was used. The endoscopist who made the decision to enroll the patient was blinded as to the treatment that would be assigned. The sphincterotomy was performed immediately after ERCP. Clearance of the CBD stones by basket retrieval or by subsequent spontaneous passage was left to the discretion of the endoscopist. Cholecystectomy was scheduled electively. Surgeons were not blinded as to the group to which the patients had been randomized. The decision to perform CBDE during the operation was based on all relevant

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considerations, including operative cholangiography. A CBDE was performed in all patients without a technically satisfactory intraoperative cholangiogram that did not show CBD stone(s). T-tube cholangiograms were performed in the early postoperative period in all patients who had CBDE. For purposes of this paper, innumerable CBD stones are defined arbitrarily as more than than 20. The accuracy of numeration beyond that point becomes questionable.

Duration of surgery in minutes and days of hospitalization from the day of surgery until hospital discharge were calculated for all patients. The cost of professional services at the adjusted prevailing rate was calculated based on Medicare allowable charges for the endoscopist, surgeon, and anesthesiologist for our Medical Service Area. Actual median duration of operation in our patients was used to calculate anesthesiology fees. Radiologist charges were not determined. The fee for interpretation of radiograms associated with ES would be approximately balanced by the additional fees for postexploration cholangiogram in patients with CBDE.

Results

Fifty-two patients completed the study. Twenty-six patients were randomized to ES&S (group 1) and 26 to SA (group 2). The patients in the two groups were comparable as to age, sex, and indication for ERCP. Multiple indications for ERCP were present in several patients. The patients were predominantly young Hispanic women without significant comorbidity. Relevant data are listed in Table 1.

The interval from ERCP to operation varied. The interval in group 1 ranged from 0 to 213 days and in group 2 from 0 to 24 days. Five patients in group 1 and four patients in group 2 underwent surgery within 48 hours of ERCP. The median time from ERCP to operation was 4 days in each group. Delays of 48 hours to 1 week after ERCP usually were due to scheduling problems. Longer delays were a result of patient refusal to proceed with surgery.

TABLE 1. *The Demographics of the Patients and the Indications for ERCP*

	ES and Surgery (26 cases)	Surgery Alone (26 cases)
Demographics		
Male:female	6:20	3:23
Mean age (years)	48.4 (31–78)	42.4 (20–86)
Indication for ERCP		
Jaundice (bili. > 2 mg. %)	17	18
Hyperamylasemia	6	3
Ultrasound positive CBD: stones or > 1 cm	14	13

Bili., bilirubin.

Exact data were not available concerning the number of cases of suspected CBD stones screened by ERCP who would have been asked to participate in the study had a CBD stone been demonstrated. A review of the endoscopy log suggests that about three patients were screened for each patient who was randomized.

Group 1: Endoscopic Sphincterotomy and Surgery

Endoscopic sphincterotomies were performed in 24 of the 26 patients. Sphincterotomy was not technically feasible in two patients. A CBDE was not performed in 14 patients with a normal intraoperative cystic duct cholangiogram. A CBDE was performed in the remaining 12 patients. These included the two patients with an unsuccessful attempt at ES. Stones were retrieved in 9 of the 12, or 35%, of the original 26 patients. In seven of these nine patients with persistent stones after ES, an attempt at clearance of the CBD by basket retrieval of CBD stones had been made during the endoscopic procedure. Operation was performed on these 9 patients from 1 to 213 days after sphincterotomy, with a median of 4 days.

Stones were not found in 3 of the 12 patients with a CBDE. In two of these three patients the surgeon did not perform a pre-exploration cholangiogram. His reasons were a serum bilirubin of 6 mg/100 mL with previous cholangitis in one patient and a common bile duct that measured 1.5 cm in diameter in the other. Regardless of the result of the cholangiogram, he intended to explore the duct. These operations were performed 5 and 12 days after ES, respectively. In the final patient with a negative CBDE, blood clots were found as an explanation for an abnormal cholangiogram. Because of scheduling feasibility, this operation was performed on the same day as the endoscopic sphincterotomy.

Three patients in group 1 had persistent stones after CBDE. In two patients the stones were documented by postoperative T-tube cholangiogram. A 21-year-old woman with innumerable CBD stones and hepatic duct stones required an emergent operation for postsphincterotomy hemorrhage from the ampulla. A duodenotomy was performed and hemostasis was secured by transduodenal sutures. The CBD was explored but the surgeon did not persist in an attempt to remove all of the intrahepatic stones in this seriously ill patient. A second patient had innumerable stones removed from the CBD and hepatic ducts at operation performed 24 hours after sphincterotomy. Completion cholangiogram was normal. The surgeon decided to rely on the sphincterotomy for passage of any residual covert stone rather than to perform a choledochoenteric anastomosis. Postoperative cholangiogram revealed a persistent stone. The third patient, also with innumerable stones in the CBD, had a normal postoperative T-tube cholangiogram. She returned several months after removal of the T tube with jaundice. Residual stones were documented by ERCP. The residual stones in all three patients were managed successfully by basket retrieval or endoscopic clearance.

Group 2: Surgery Alone

Cystic duct cholangiogram was normal in three patients and a CBD exploration was not performed. Common bile duct exploration was performed in the remaining 23 patients. Common bile duct stones were present in 19, or 73%, of the original 26 patients. Stones were not found in four patients at CBDE. The surgeon decided against pre-exploration cholangiogram in two of these four patients because of the positive ERCP that was performed 4 and 6 days earlier, respectively. A third patient had a total bilirubin level of more than 10 mg/100 mL immediately before operation and the final patient had a CBD that measured 2 cm in diameter. In both of the latter patients, the surgeon was unwilling to omit common bile duct exploration, regardless of the results of cholangiography.

Three of the twenty-six patients (12%) in group 2 had persistent stones after CBDE. This represented 16% of the patients with stones in group 2. Two of these three patients had innumerable stones removed from the common bile duct and hepatic ducts during the operation. Completion cholangiograms were negative in both of these patients. The surgeon elected not to perform an operative choledochoenteric drainage but rather to rely on radiologic or endoscopic intervention after operation for any residual covert stones. A postoperative T-tube cholangiogram revealed residual stones in each patient. These were successfully managed by basket retrieval or endoscopic clearance. A third patient with 12 stones at operation had a normal postoperative T-tube cholangiogram. At the time of his death 18 months later from colon cancer, autopsy revealed a CBD stone.

Data regarding status of stones in the CBD at various times in the study are depicted in Table 2. The end point of the study was designed to be stones present at operation in group 1 and after the operation in group 2. The 35% incidence of persistent stones after ES as compared to a 12% incidence after CBDE in group 2 is significant by Fisher's exact test, with a p value less than 0.05. For purposes of statistical analysis, patients were left in the original group to which they were randomized.

Complications

Hyperamylasemia developed in three patients in group 2 after ERCP but resolved in each patient within 72 hours. There was one episode of major hemorrhage in each group. The case of hemorrhage after ES in group 1 that required emergency celiotomy has already been discussed. A patient in group 2 had a dense inflammatory process with a cholecystoduodenal fistula identified during operation. The fistula was not seen during endoscopy. The fistula was closed. The patient bled after operation and required re-exploration with religation of the cystic artery.

TABLE 2. *The Number of Cases with Stones in the CBD at Various Times During the Study*

	ES and Surgery No. Pts. (%)	Surgery Alone No. Pts. (%)
At ERCP	26 (100%)	26 (100%)
	Sphincterotomy	
At operation before CBDE	9 (35%)*	19 (73%)
At follow-up	3 (12%)	3 (12%)*

* p = <0.05.

There were no deaths in either group. Other complications were one minor hemorrhage from the papilla in one patient from group 1 and one from the wound in one patient in group 2, a minor wound infection that occurred in a patient in each group, a sacral decubitus in a patient in group 1, and a forearm rash in a patient in group 2.

A major complication occurred in a patient being screened for participation in the study, but not as yet randomized. A 50-year-old woman had been admitted to the hospital with gallstone pancreatitis. After the serum amylase returned to normal and clinical manifestations of pancreatitis resolved, she underwent ERCP. A duodenal perforation occurred and emergency celiotomy was performed with closure of a 15-mm perforation. Cholecystectomy and CBDE were performed. One stone was retrieved from the CBD.

Endoscopic Sphincterotomy Versus *CBDE*

The success of ES or CBDE in clearing the CBD of stones was calculated by comparing the result of ES in patients with CBD stones documented by ERCP immediately before ES with that of CBDE that was performed in cases with proved stones during operation from either group. Seventeen of twenty-six patients (65%) were stone free after ES as documented by subsequent intraoperative cholangiography. Seventy-nine per cent of the 28 patients with documented stones at the time of operation were stone free after operation. Five of the six patients with residual stones after CBDE had innumerable CBD stones (Fig. 1). The above calculations represent cross-over from original randomization and two disparate populations of patients. It was concluded that a study of a statistical difference between these two populations would not be valid.

Time Considerations

The median duration of operation in patients randomized to group 1 (ES&S) was 151 minutes, with a range from 80 to 300 minutes. The median duration of hospi-

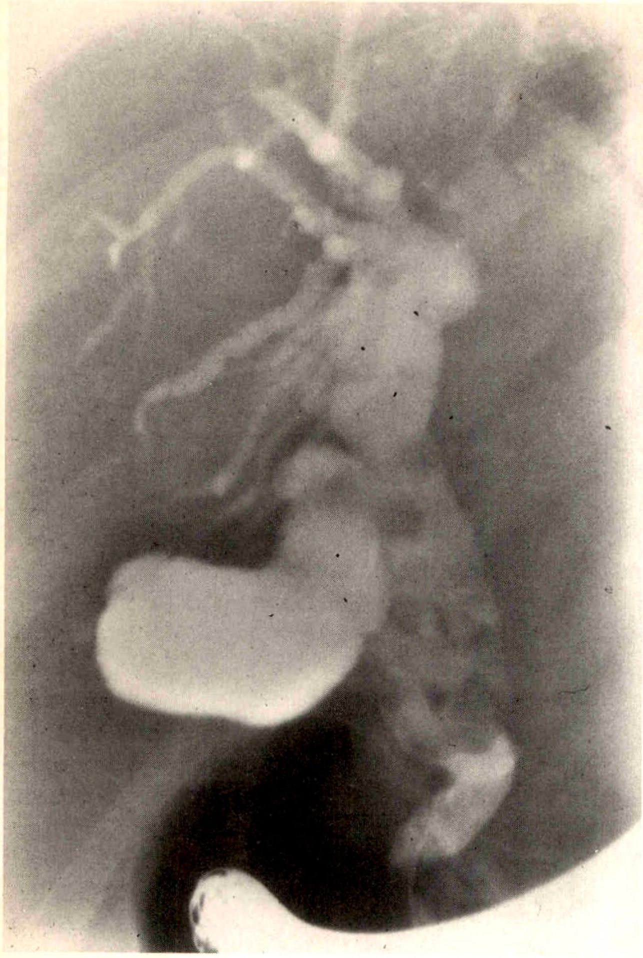

FIG. 1. This cholangiogram was obtained at the time of ERCP and reveals innumerable CBD stones. The patient was randomized to ES. There were two residual stones in the CBD at the time of the operation, which was performed 48 hours later.

talization in group 1, beginning with the day of surgery, was 5 days, with a range from 2 to 19 days. The median duration of operation in patients randomized to group 2 (SA) was 214 minutes, with a range from 115 to 420 minutes. The median duration of hospitalization in this group was 6 days, with a range from 4 to 22 days.

The duration of hospitalization from the day of surgery in patients with successful ES and who did not require CBDE ranged from 2 to 12 days, with a median of 5 days. The comparable figures for patients from either group who underwent CBDE were a range of 4 to 22 days and a median of 7 days.

Professional Cost

Professional fees for the endoscopist, surgeon, and anesthesiologist as calculated for Medicare reimbursement for a typical case are depicted in Table 3. For a patient with successful ES who did not require CBDE, the professional fees totaled $2952.00 and those for a patient undergoing cholecystectomy and CBDE the fees were $2740.00.

Discussion

Endoscopic sphincterotomy was first described in 1974 independently by Classen and Demling in Germany,[8] and Kawai from Japan.[9] Sphincterotomy initially was used for patients with recurrent or retained CBD stones after cholecystectomy with or without CBD exploration.[10,11] As experience grew the application of sphincterotomy in the management of CBD stones was advocated in high-risk patients,[12] patients with cholangitis,[13] and patients with acute biliary pancreatitis.[14] Endoscopic sphincterotomy to permit stone passage has been suggested as an alternative to cholecystectomy in patients with cholecystolithiasis with or without choledocholithiasis and with or without a patent cystic duct[4,15–18] or as a method for managing choledocholithiasis before elective surgery in patients with synchronous cholecystolithiasis and choledocholithiasis.[19,20] The latter indication is the subject of this study and has been the basis for one previous randomized study.[21]

Reports of the efficacy of ES in clearing the CBD of stones are as high as 90%.[22] Cases with basket retrieval or the use of other techniques for clearance of stones as well as those with spontaneous passage are included. Most studies report a percentage of clearance at the completion of the initial procedure, whereas others calculate the percentage based on multiple endoscopic procedures.[20,21] Few studies have verified that the ducts are stone free by subsequent cholangiography. Surgeons are well aware that cholangiography at the completion of CBDE may not reveal calculi, whereas the postoperative cholangiogram will reveal residual stone.

The literature on the efficacy of CBDE in clearance of CBD stones is also somewhat confusing. Reports may state the percentage of residual stones by postoperative cholangiogram of all patients who had a CBDE or only among those with a CBDE whose ducts harbored stones. Way and associates[23] reported a 7% incidence of retained

TABLE 3. *The Cost of Successful ES and Cholecystectomy Compared to that of Cholecystectomy and CBDE*

Successful ES and Surgery			Cholecystectomy and CBDE
Hospital			
>Preop. Days for ES		=	>Postop. Days for CBDE
Endoscopy Suite		=	>OR Time
Professional fees			
Endoscopist	$800		
Surgeon	$1312		$1680
Asst. surgeon	$328		$420
Anesthesiologist	$512		$640
Total	$2952		$2740

stones, a rather typical figure. This was for all cases of CBD exploration. The incidence among cases with choledocholithiasis was 10%. In a series reported subsequent to the introduction of intraoperative choledochoscopy, Felliciano and associates[24] reported a 8.9% incidence of retained stones in patients with CBDE who had ductal stones. Glenn,[25] in a collected series from various clinics of 16,700 cases of CBDE, reported a 4.3% incidence of retained CBD stone. The rate among cases from whom stones were removed was 9.5%. Thus a figure of about 10% for the incidence of retained stones by postoperative cholangiogram among patients with CBD stones at operation probably is a reasonable estimate.

Experienced surgeons know that the risk of retained stones is vastly increased in patients with innumerable stones in the common and hepatic ducts. A negative completion cholangiogram too often fails to reveal a covert stone lurking in an hepatic duct that is demonstrated on a postoperative cholangiogram. Cotton[22] has emphasized the hazards inherent in attempting to compare reported results within and between groups of patients treated by ES or CBDE.

In this study a significantly greater number of CBD stones were present at surgery in cases randomized to preoperative ES than in patients randomized to surgery alone. This was the intended end point of the study. The incidence of residual stones among patients undergoing ES also was higher than that of all patients in the study who underwent a CBDE and in whom stones were present.

There are hazards in interpretation of this data with respect to residual stones. Seven patients in whom stones were documented at the time of ERCP and who were randomized to surgery alone did not have stones in the CBD at the time of operation. Presumably the stones were passed spontaneously between ERCP and the day of operation. Credit is given to ES for clearance of stones in all patients undergoing ES and in whom stones were not present at the time of operation (17 patients). A number of these patients might have passed these stones spontaneously without endoscopic sphincterotomy. Finally stones present in the CBD after sphincterotomy could represent stones that passed from the gallbladder to the CBD after ES and successful clearance of the CBD and in the interval between ES and surgery. We assumed that all CBD stones present at surgery and after ES were failures of ES.

This study demonstrates the challenge in management of innumerable CBD stones. Three patients from each group had residual stones at the completion of the study. Five of these six patients had innumerable CBD stones. When 20 or more stones are removed from the CBD, one or more additional stones are likely to be present. Formerly such cases were considered during the first operation for a drainage procedure to permit subsequent passage of residual stones. Controversy existed as to whether the preferable procedure was a choledochoduodostomy, choledochojejunostomy, or transduodenal sphincteroplasty. With the advent of basket retrieval and ES, such drainage procedures are less frequently used at the first operation.[22,26] As in the cases in this study, the surgeon is more prone to rely on postoperative basket retrieval or transduodenal endoscopic procedures for retrieval of residual stones. Such procedures were successful in our patients with retained stones after surgery.

Complications of ES were significant. They included three instances of hyperamylasemia, one episode of major hemorrhage, and one episode of duodenal perforation in a patient screened but not randomized to the study. Conversely there was one major episode of hemorrhage in the SA group.

There were no deaths among our patients. This is consistent with experience with either cholecystectomy and CBDE or ES in good-risk patients. With either of these procedures the mortality risk should not exceed 1%.[19,22,27,28] A policy of ES before surgery could not be expected to effect favorably this low mortality rate from cholecystectomy and CBDE in good-risk patients, and indeed the cumulative mortality from both procedures might be higher than that for either alone.

Our results must be compared with those reported by Neoptolemos and associates[21] in their randomized study of ES and surgery or surgery alone in cases similar to ours. They randomized twice as many cases. The interval between endoscopy and surgery varied widely as in our patients. The definition of successful ES and stone clearance was a clear duct, as judged by the endoscopist, at the end of the endoscopic procedure rather than findings at subsequent operation, the end point of our study. Cholangiograms performed at the time of ES were assumed to be 100% accurate, a most questionable assumption. Five patients refused surgery after ES and had no further objective confirmation of the success of ES. One patient, defined as a success for ES, required more than one endoscopic procedure for stone clearance. The paper does not state whether at operation every case had either a negative cholangiogram or a CBDE. In two 'successful' cases of ES, CBD stones were present at the time of operation. The stones in these patients were assumed to have passed from the gallbladder to the common duct in the interval between ES and surgery. We considered all CBD stones at surgery to represent failure of ES. Thus their figure of 91% success for ES cannot be compared with our figure of 65%, and such an attempt would epitomizes Cotton's[22] caution of comparing "apples and oranges."

Major complications reported by Neoptolemos[21] were more frequent in patients with ES than in those with SA. A review of their data leads to the conclusion that the severity of the major complications also was greater with

ES. This is consistent with our experience, although our overall rate of complications was low in both groups.

The actual costs of all hospitalization were not compared among the patients randomized to the two arms of this study. Variations in duration of hospitalization that were due to nonmedical reasons, such as scheduling for endoscopy and surgery, surgeon and endoscopist availability, and patient vacillation to accept surgery, would make such determinations meaningless. The duration of hospitalization from the day of surgery was compared between the two randomized groups as well as between those patients who did and did not require CBDE. The median duration of additional hospitalization in patients randomized to SA was 1 day and in all cases of CBD exploration was 2 days. The additional postoperative hospitalization with CBDE would be offset in a patient with ES&S by the preoperative hospitalization associated with the endoscopic procedure. The added operating room charges for a CBDE would be offset by the facility fee for the endoscopy suite used for the ERCP and ES. Our estimate of professional fees for these two approaches to the management of synchronous cholecystolithiasis and choledocholithiasis on an elective basis reveal that the charges would be marginally greater for the endoscopist, surgeon, and anesthesiologist in patients undergoing successful ES followed by cholecystectomy then would be true of the patient undergoing cholecystectomy and CBDE. In conclusion, for an individual patient who underwent a successful ES before surgery, the facility and professional costs would be about equal for the two approaches. Van Stiegman and associates[29] compared two groups of nonrandomized and questionably comparable cases and concluded that preoperative ES would be cost-effective. Their cases with CBDE were hospitalized an additional 4.4 days at $1085.00 per day. If this seemingly excessive duration of hospitalization had not occurred there would not have been a cost benefit.

Despite the above conclusion regarding an individual case of successful ES&S, a general policy of ERCP and ES before elective surgery in the management of patients with cholecystolithiasis and suspected choledocholithiasis would be much greater than that for SA because of the screening costs necessary to identify patients with CBD stones. An extensive literature exists with respect to the yield in identification of CBD stones that may be anticipated at elective surgery based on various indicators such as jaundice, previous pancreatitis, dilated duct, or palpable stones.[23] These studies establish that a minority of patients with other than a palpable stone will harbor a CBD stone at the time of operation. Thus if one were to screen patients using our indications, namely, a serum bilirubin level greater than 2 mg/100 mL, a dilated duct by ultrasound, and a history of hyperamylasemia, one would predict confidently that not more than one in three patients would be identified with CBD stones. In addition CBDE would still be required for those patients in whom ES failed to clear the ducts. The total cost of the program would be much greater.

The results of this study do not support the routine use of ES as a preoperative procedure for removal of CBD stones in patients with cholecystolithiasis and choledocholithiasis who are candidates for elective surgery. Neither efficacy in clearing the CBD of stones, morbidity of the procedure, nor cost would favor a preoperative endoscopic sphincterotomy. These conclusions are similar to those of Neoptolemos and associates[21] based on their randomized study. These conclusions should not be applied to other indications for ES. The results of our study are not relevant to the role of ES in patients with severe acute gallstone pancreatitis, cholangitis, retained stone after previous biliary surgery, or to the treatment of patients with high surgical risk. They should not be applied to a patient with obstructive jaundice who undergoes an ERCP to determine whether obstruction is due to stone or tumor. A stone may be identified in the common bile duct. It is reasonable under such circumstances for an ES to be performed to permit passage of the stone. Preferably 48 hours should lapse between ES and surgery to allow the passage of any residual stone(s). The result of a cholangiogram performed at the time of ES should not be accepted. The surgeon should perform an intraoperative cholangiogram. Finally there is current intense interest in laparoscopic cholecystectomy.[2] The management of CBD stones in patients selected for that procedure has not been standardized. The results in clearance of the CBD of stones that we report can be a part of the debate that will occur as to whether laparoscopic cholecystectomy might be preceded or followed by ES.

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Discussions

Dr. Ronald K. Tompkins (Los Angeles, California): Dr. Donovan and his coauthors are to be congratulated for designing a prospective randomized trial comparing endoscopic papillotomy to operation for the treatment of patients with common duct stones.

Their findings were that 35% of the patients treated by endoscopic papillotomy had residual common duct stones, proved at operation, a median of 4 days after procedure, compared to the 12% of surgically treated patients who had residual common duct stones at the time of postoperative T-tube cholangiogram.

Clearly, in the author's institution, a patient with common duct stones who is treated by operation is three times less likely to have residual common duct stones than the patient treated by endoscopic papillotomy.

However, if the patient treated by endoscopic papillotomy for common duct stones then undergoes subsequent cholecystectomy and is found to have common duct stones, that patient has a 33% chance of having postoperative retained stones. That is, three of nine of their patients with stones in group 1 had retained stones at the end of the operation. Why should the residual postoperative stone rate be twice as high in that group as it was in group 2, which was only 16%; 3 of 19 patients who underwent operation with stones in the common duct?

The authors suggested that complications of papillotomy and unwise reliance by the surgeon on previous ERCP and papillotomy may be major factors. The question logically arises as to whether biliary endoscopy was used in all these patients, and in both groups was completion T-tube cholangiography performed at the end of the procedure?

Studies from a number of institutions, our own included, have demonstrated the ability of operative choledochoscopy or cholangioscopy and completion cholangiography to reduce residual common bile duct stones to less than 2%, often to zero.

Undoubtedly the endoscopists who read this paper will argue that more time should have been given to the papillotomy patients to pass their stones before operation. However some of the patients, as Dr. Donovan has noted, went as long as 213 days before operation after the papillotomy was done. So I do not think that is a very good argument.

The real question is whether in nonemergent patients with common duct stones it makes sense to subject them to a preoperative ERCP and papillotomy before removing their gallbladders. It does not make sense to compound the risk to the patient by performing two procedures, that is, endoscopic papillotomy and then adding cholecystectomy and common duct exploration when the latter procedure has a better success rate as demonstrated by the authors.

They have presented a wealth of data in their manuscript and, like all good studies, it raises more questions for future work. I would ask them, in addition, if they had any patients with unusual biliary problems in this series, such as the oriental cholangiohepatitis patients that they have described before, and what were their exclusion criteria for this study.

Also how many endoscopists and how many surgeons participated in the procedures?

Dr. Talmadge Bowden (Augusta, Georgia): I find this to be a very well-designed study that, unfortunately, in view of recent endoscopic advances, may be a bit obsolete.

I agree with Dr. Tompkins that the 65% stone clearance rate by endoscopic papillotomy is too low. As you know, you should expect an 80% to 90% clearance rate.

I, too, want to know if you, in your hospital routine, do intraoperative choledochoscopy, which is clearly an additional marriage of endoscopy to surgery that is very worthwhile?

Dr. Donovan, in reviewing your bibliography, I noted that there were three studies that you did not reference. Because these studies do support the thesis that preoperative endoscopic sphincterotomy may be of benefit, let me briefly summarize them.

Worthley from Australia compared common duct exploration in 102 patients with endoscopic sphincterotomy and 50 patients with surgery and found 26% fewer complications after sphincterotomy than after common duct exploration. He also showed a clear difference in mean hospital stay, with sphincterotomy being 3 days and surgery alone 7 days.

Heinerman studied 728 patients in whom ERCP and stone extraction were performed 2 to 4 days before cholecystotomy. These authors reduced their complication rate from 21% to 2% and the residual stone rate was reduced from 2.2% to 0.5%. Mortality rates were also reduced.

Poncion from Lyon, France, found that preoperative endoscopic sphincterotomy reduced residual stone rate and decreased the length of hospitalization.

Clearly the concept of preoperative endoscopic sphincterotomy has merit and should be evaluated further and joined with laparoscopic cholecystectomy and laparoscopic common duct exploration.

This will probably be the sequence of events and is the sequence of events in America today. If common duct stones are suspected, the patient undergoes ERCP and then goes to laparoscopic cholecystectomy. During surgery a decision would be made as to whether further common duct exploration would be of benefit on the basis of intraoperative cholangiography.

If a common duct stone is found during laparoscopic cholecystectomy, most patients then will be subjected to endoscopic sphincterotomy, either late that afternoon or the next day. I believe this is what we are going to now.

DR. ROBERT HERMAN (Cleveland, Ohio): Dr. Donovan and his colleagues have brought up a number of issues in this interesting paper. The effectiveness of endoscopic sphincterotomy, the efficacy of common bile duct exploration, the problem of appropriate management of the patient with more than 20 bile duct stones and, finally, the cost of ERCP and endoscopic sphincterotomy and its value before a cholecystectomy when bile duct stones are suspected by preoperative studies.

The manuscript goes into all of these issues in detail. Their results show that endoscopic sphincterotomy is not always effective. As mentioned 35% of patients still had stones in the bile duct at operation in group 1, randomized to endoscopic sphincterotomy and surgery. Furthermore it had some significant complications—hemorrhage, a perforation, and hyperamylasemia in three patients.

While operative bile duct exploration also was not completely effective in removing all bile duct stones, at least a T tube could be placed and the retained stones removed later through the tube.

Also, as implied in the manuscript, when more than 20 stones are found in the bile duct, there is a good argument for considering a choledochoduodenostomy in addition to the bile duct exploration.

In fact our data from Cleveland would indicate that if more than five stones are found in a dilated bile duct, choledochoduodenostomy should be considered.

In regard to the costs, if all patients with suspected bile duct stones had preoperative ERCP, this alone would add to the costs of these procedures. Interoperative cholangiography will give the same information faster and cheaper.

The only time I would recommend preoperative ERCP and preoperative endoscopic sphincterotomy in patients suspected of having bile duct stones, I believe, as Dr. Bowden mentioned, would be in patients scheduled for laparoscopic cholecystectomy.

In this group of patients it seems to make some sense and may be cost-effective. I wonder if Dr. Donovan would comment further on this group of patients.

DR. WILLIAM NEALON (Galveston, Texas): As the other discussants have mentioned, a 35% rate of stone retention after endoscopic sphincterotomy and stone extraction is far in excess of any of the many large series that have been reported on that procedure. I was wondering if the authors, aside from stone number, have discussed with their endoscopic colleagues the technical features that might account for that high note.

The previous discussants also mentioned the combination of this procedure with laparoscopic cholecystectomy. That is very clearly one that makes this discussion very pertinent. Use of preoperative endoscopic sphincterotomy can be easily coupled with that operation.

Pertinent to that concept, I wonder if the authors have a logic for the delay by having a relatively prolonged time after the endoscopic sphincterotomy before their operations. Possibly some of the costs that they have encountered by an otherwise separate admission or perhaps by a prolonged hospitalization caused by a delay after the endoscopic procedure before they have their operation might be overcome by simply proceeding, even the next day, to operation after their endoscopic sphincterotomy. Could comment on your reasons for delay?

DR. ARTHUR J. DONOVAN (Closing discussion): Several people have commented with respect to the incidence of retained stones after the endoscopic papillotomy. There was an excellent article by Dr. Cotton, in which he discussed 'apples and oranges,' and the problem of comparing dissimilar groups of patients and dissimilar criteria for determining success rates of either papillotomy or surgery. In studies that report a 90% success rate with sphincterotomy, that rate is not verified by subsequent cholangiography. It is based on the conclusion of the endoscopist at the completion of the procedure. Every surgeon in this room knows the fallacy of the completion cholangiogram at the time of surgery. In patients with stones that were present in the ducts after his 'successful' papillotomy, Neoptolemos assumed that they had passed from the gallbladder into the duct in the interval between papillotomy and surgery. We assumed any stone in the duct to have been one that we left behind. I do not think you can compare the figures. The discussants have commented with respect to the number of retained stones. Five of six of these postoperative instances were in the group of patients with more than 20 stones that Dr. Herman discussed. There is a dearth of information about the exact incidence of retained stones as related to the numbers of stones removed at the time of surgery. Every one of us knows that when you remove 20 to 25 stones from the common bile duct, it is very likely that there is an additional stone.

With respect to Dr. Tompkins' question, we routinely use choledoscopy and completion cholangiography. The questionable cholangiogram that I mentioned was the patient who required emergency celiotomy for control of papillotomy hemorrhage.

The surgical procedures were performed by a variety of attending surgeons and surgical residents. The sphincterotomies were done by fellows in gastroenterology supervised by either one or two of the attending staff in gastroenterology.

We did not use exclusion criteria. This study would probably raise a question as to whether we should have used some exclusion criteria in terms of the numbers of stones and the magnitude of the calculus disease present in the biliary ductile system in patients who would be included in the study.

To address the question of the relationship of this study to the explosion of interest in laporoscopic cholecystectomy, it is clear, as was pointed out by both Dr. Bowden and Dr. Nealon, that the results of this study can bear relationship to the patient who is to undergo laparoscopic cholecystectomy who harbors a stone in the common bile duct.

It would be appropriate to re-emphasize that this study only relates to one indication for endoscopic sphincterotomy, as a preoperative procedure in patients having elective surgery. The results should not be applied to other indications and uses of this procedure. Endoscopic sphincterotomy is probably one of the most valuable therapeutic modalities that I have seen introduced.

Choledochoduodenostomy

Analysis of 71 Cases Followed for 5 to 15 Years

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To investigate the long-term effectiveness of choledochoduodenostomy (CDD), the experience with 71 patients followed for 5 or more years after CDD was analyzed retrospectively. From 1968 to 1984, 134 patients underwent CDD. Eight patients (6%) died in the immediate postoperative period, 55 left the hospital, 8 of them were lost to follow-up, and 47 were followed but died before 5 years elapsed after CDD. The remaining 71 patients form the data base for this analysis: 38 were followed for more than 5 years, 25 were followed for more than 10 years, and 8 were followed for more than 15 years ($\bar{x}$ 12.1 years ± 1.3 SEM). Choledocholithiasis, chronic pancreatitis, and postoperative stricture were the indications for CDD. Cholangitis was observed in only three patients. The diameter of the common bile duct (CBD) was large in most patients ($\bar{x}$ 18 mm ± 0.9 SEM). These results infer that CDD is effective to treat non-neoplastic obstructing lesions of the distal CBD on a long-term basis and that the presence of a dilated CBD (more than 16 mm) that allows the construction of a CDD more than 14 mm is essential to obtain good results.

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IN THE PAST decade, written communications about choledochoduodenostomy (CDD) have appeared with increasing frequency in journals published in the United States. Most of them are from American surgeons[1-9] documenting their increasing interest and factual experience with this procedure. There are also several series of CDD analyzed by surgeons from Europe,[10-15] Israel,[16-18] and Latin America.[19] With all this information, the indications for constructing a CDD to treat obstructions of the distal common bile duct (CBD) have been better defined.

Furthermore the advantages offered by this procedure, as well as its risks and disadvantages, also have been well noted in most of the already quoted bibliographic references. However, with two exceptions,[12,20] the long-term results of CDD, particularly in reference to the incidence of complications such as cholangitis and the 'sump syndrome,' have not been documented clearly.

This review analyzes the results observed in a group of patients who underwent CDD, mostly for non-neoplastic obstructive lesions of the distal CBD, who were followed for a minimum of 5 years.

Materials and Methods

The records of all patients who had an anastomosis surgically constructed between the common hepatic bile duct (CHBD) or the CBD and the first or second portion of the duodenum during a period of 17 years from 1968 to 1984 at the University of Alabama and Veterans Administration Hospitals were reviewed retrospectively. There were 134 such patients. Eight of them (6%) died after operation; the other 126 patients left the hospital alive but eight of them (6%) were lost to long-term follow-up. The remaining 47 (35%) died 6 or more months after their CDD. The remaining subgroup of 71 patients was followed for 60 or more months. They were alive at the time of completion of this study (January 1990) and constitute its patient data base (Fig. 1). Most of them were followed as outpatients with regularly scheduled visits every 6 to 12 months. At the time of this study, the information was updated by personal interview or *via* telephone in 59 patients, and with their relatives in the other 12. The usual statistical methods were used to determine the likelihood that the differences were due to chance.

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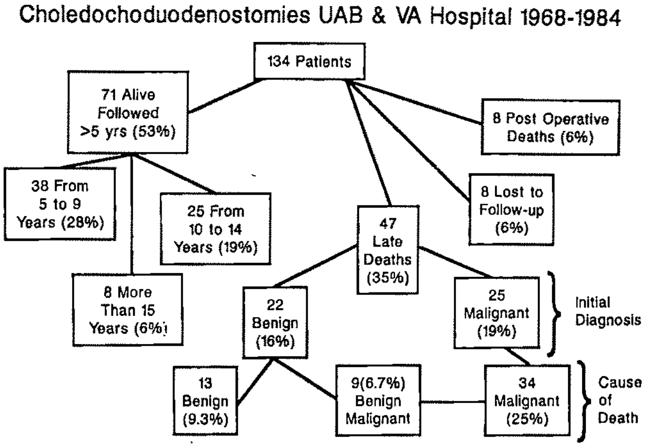
Choledochoduodenostomies UAB & VA Hospital 1968-1984
134 Patients
71 Alive Followed >5 yrs (53%)
8 Post Operative Deaths (6%)
38 From 5 to 9 Years (28%)
25 From 10 to 14 Years (19%)
8 More Than 15 Years (6%)
47 Late Deaths (35%)
8 Lost to Follow-up (6%)
22 Benign (16%)
25 Malignant (19%)
Initial Diagnosis
13 Benign (9.3%)
9(6.7%) Benign Malignant
34 Malignant (25%)
Cause of Death

FIG. 1. Outcome of 134 patients who underwent choledochoduodenostomy. The 71 who survived 5 or more years comprise the patient data base of this analysis.

Results

Main Patient Data Base (Cases Followed for 5 or More Years)

Of the 71 patients who survived CDD for 5 or more years, 37 are men (52.1%) and 34 are women (47.9%); their ages ranged from 21 to 95 years (x̄ 59.5 ± 2.0 years SEM).

Depending on the length of their follow-up period after CDD, these patients were categorized as follows: group A, followed from 5 to 9 years; group B, followed from 10 to 14 years; and group C, followed for 15 or more years (Table 1). The indications for the CDD were choledocholithiasis in 40 (56.3%), chronic pancreatitis with choledocholithiasis in 9 (12.7%), chronic pancreatitis without choledocholithiasis in 14 (19.7%), and postoperative strictures in 8 (11.3%). An elevated level of total bilirubin in serum (more than 1.5 mg/100 mL) was found in 61 patients (86%). The levels of alkaline phosphatase in serum ranged from 53 to 910 international units (IU) (x̄ 567 ± 2.8 SEM). The diameter of the common bile duct, as recorded in the operative note, ranged from 8 to 47 mm (x̄ 18 mm ± 0.9 SEM). This information is categorized by groups in Table 2.

The technical variations of the CDD were side-to-side (S-S) in 67 patients (94.3%) and end-to-side (E-S) in four patients (5.7%). In six of these cases (8%), the main hepatic duct rather than the CBD was used (Table 3). In only two cases (2.8%), a tubular stent was left through the CDD.

There were 22 complications observed in 20 patients (28%) within the 30 days following operation. Wound infection that occurred in eight (11%) was the most common. The other observed postoperative complications are summarized in Table 4.

There were three cases (4.2%) of proved cholangitis documented by fever of more than 38° C, associated with chills, elevated total bilirubin (more than 4 mg/dc), and elevated alkaline phosphatase (more than 200 IU). All of these three patients survived their CDD 15 or more years (group C) and their episodes of cholangitis warrant description. The first patient underwent CDD in 1971 to correct a postoperative stricture of the CBD; the constructed CDD measured only 12 mm in diameter. Five years after operation in 1976, she had two episodes of cholangitis that lasted 2 and 4 days, respectively. She was treated with intravenous antibiotics and never again developed signs or symptoms of bacterial cholangitis; she remains well in 1990.

The second patient has been followed since 1972. He required a CCD that was 10 mm in diameter to correct a stricture of the CBD secondary to an operative injury. Two years later he developed an active duodenal ulcer that partially obstructed the CDD resulting in jaundice, fever and chills. The duodenal ulcer was treated medically and the signs and symptoms of cholangitis subsided. In the subsequent 15 years, this patient had 21 similar episodes; the last one in 1989 persisted for 2 weeks and was due to fibrous stenosis of the CDD, assumedly from the multiple process of healing the duodenal ulcer that always occurred next to the CDD. This was resolved with the insertion of a metallic expandable stent placed percutaneously. This patient has remained asymptomatic for the last 5 months.

The third patient was operated on in 1973 at age 29 years with the presumptive diagnosis of choledocholithiasis. At operation she was found to have sclerosing chol-

TABLE 1. *Demographics of 71 Patients Who Underwent Choledochoduodenostomy and Were Followed for More than 5 Years*

Group	Follow-up (years)	Mean Follow-up (years)	No. of Pts.	Sex M	Sex F	Mean Age (years ± SEM)
Group A	5–9	7.3 ± 1.1*	38 (53.5)†	22 (58)	16 (42)	61 ± 2.7
Group B	10–14	12.3 ± .85	25 (35.2)	11 (44)	14 (56)	58 ± 4.1
Group C	>15	16.5 ± .2	8 (11.3)	4 (50)	4 (50)	56 ± 7.1
Total		12.1 ± 1.3	71 (100)	38 (53.5)	34 (46.5)	59 ± 2.2

* ± SEM, standard error of the mean.
† Percentage.

They are categorized in three groups A, B and C, depending on the length of their follow-up period.

TABLE 2. *Indications for Choledochoduodenostomy and Estimated Diameter of the Common Bile Duct Recorded at the Time of Operation*

Group	CBD Lithiasis	Lithiasis and CP	Chronic Pancreatitis	Postoperative Stricture	Mean Diameter of CBD
Group A (n = 38)	23 (60.5)	2 (5)	10 (26.3)	3 (7.9)	18* ± 1.2†
Group B (n = 25)	14 (56)	6 (24)	2 (8)	3 (12)	21 ± 0.8
Group C (n = 8)	3 (37.5)	1 (12.5)	2 (25)	2 (25)	14 ± 0.7
Total (n = 71)	40 (56.3)	9 (12.7)	14 (19.7)	8 (11.2)	18 ± 0.9

* mm.
† ±standard error of the mean.

CP, chronic pancreatitis.
Numbers in parentheses are percentages.

angitis proved by biopsy and a CDD that measured 12 mm was constructed. Six months later she began to have episodes of cholangitis with fever and chills that were treated with oral and intravenous antibiotics. She eventually died in 1988 from liver failure; there were 35 recorded episodes of cholangitis for this patient.

Although at the time of construction of the CDD choledocholithiasis was found in 49 patients (69%), recurrent choledocholithiasis was not apparent in any of the 71 cases analyzed. In 40 patients (56%), cholecystectomy was done at the time of the CDD. In the remaining 31 cases (44%), the gallbladder had been removed previously. In 26 patients (84%) of this subgroup with absent gallbladders at the time of CDD, biliary calculi were removed from the lumen of the CBD; choledocholithiasis was not found in 5 patients (16%) from this group. A stenotic ampulla of Vater, as judged by the the operating surgeon's inability to pass a calibrated dilator size 3 mm or larger into the duodenum, was found in 68 (96%) of the 71 patients. All of the three patients in whom ampullary stenosis was not found had cholecystectomy before the CDD.

Patients Not Followed for More Than 5 Years

Postoperative deaths. Eight patients died in the hospital during the same hospitalization for their CDD. Five of them were operated on because of malignant neoplastic diseases of the pancreas and the bile ducts and they died of postoperative complications. In two patients, the CDD was done as a desperate attempt to reconstruct their biliary system that had been injured in previous operations performed at other hospitals; both of these patients had subhepatic abscesses; both died of sepsis and multiple-organ system failure.

The remaining patient was operated on for acute cholecystitis and choledocholithiasis and had advanced cardiovascular disease with severe coronary artery occlusive disease. She died on the seventh postoperative day of intractable arrhythmias. The demographics, the initial diagnosis, and the cause of death for these patients are shown in Table 5.

Patients lost to follow-up. Despite a persistent search, there were eight patients in whom adequate long-term follow-up could not be obtained. Six of them had been operated on at the Birmingham Veterans Administration Hospital and shortly after their operation moved to another state. Their records were removed from our Veterans Administration Hospital and subsequently could not be located. All of these six patients left the hospital in good conditions with normal liver function tests, so it is presumed that their operation was initially successful.

Two other patients were operated on at the UAB Hospital; one was free of symptoms on an outpatient visit 5 months after CDD, but subsequent follow-up could not be obtained. The other patient left the hospital in good condition on the eighth postoperative day and was lost to follow-up. The details of these eight patients are summarized in Table 6.

TABLE 3. *Type of Anastomosis Used in 71 Cases of Choledochoduodenostomies* Followed for 5 or More Years*

Group	Side–Side (S–S)	End–Side (E–S)
Group A	36	2
Group B	24	1
Group C	7	1
Total	67	4

* Six hepaticoduodenostomies are included.
S–S, 1.
E–S, 5.

TABLE 4. *Postoperative Complications Other than Cholangitis Observed in 71 Patients with Choledochoduodenostomies*

Specific Complications	Group A	Group B	Group C	Total
Pneumonia	1	—	1	2 (2.7%)
Athelectasis	—	3	—	3 (4.1%)
GI bleeding	—	—	1	1 (1.4%)
Pancreatic fistula	1	—	—	1 (1.4%)
Biliary fistula	1	—	—	1 (1.4%)
Postoperative fever	1	—	—	1 (1.4%)
Wound infection	5	3	—	8 (11.1%)
UT infection	2	2	—	4 (5.6%)
Rash	—	1	—	1 (1.4%)
Total	10	9	3	22

GI, gastrointestinal; UT, urinary tract.

TABLE 5. *Demographics, Diagnosis, and Cause of Death of Eight Patients Who Died After Choledochoduodenostomy*

Patient	Age (years)	Sex	Death PO Day	Initial Diagnosis	Cause of Death
1	64	M	7	Acute cholecystitis and CBD stones	Arrhythmia
2	39	F	55	Postop stricture	Sepsis, MOSF
3	61	F	17	Postop stricture	ARDS
4	29	M	9	Pancreatic carcinoma	DIC
5	65	M	12	Chronic pancreatitis and pancreatic carcinoma	ARDS
6	57	F	10	Cholangiocarcinoma	Sepsis, MOF
7	86	F	18	Pancreatic carcinoma	ARDS
8	66	F	12	Pancreatic carcinoma	Liver failure

MOSF, multiple-organ systems failure.
ARDS, adult respiratory distress syndrome.
DIC, disseminated intravascular coagulation.
PO, postoperative.

Late deaths. Of the remaining 47 patients (35%), the initial diagnosis of benign disease was made in 22 and of a malignant neoplastic process in 25. All of the 47 patients died 3 to 58 months after their CDD (x̄ 16.5 months ± 2.3 SEM). In 34 patients the cause of death appeared to be directly related to a malignant neoplasm, which included pancreatic carcinoma in 29, ampullary carcinoma in 1, colonic carcinoma in 1, Hodgkin's lymphoma in 1, prostate carcinoma in 1, and cholangiocarcinoma in 1. The mean survival period in these 34 patients was x̄ 0.9 years ± 3 SEM. It should be noted that nine patients initially coded as having benign disease at the time of their CDD subsequently died from carcinoma. Therefore we could speculate that in some of these patients, particularly those who had carcinoma of the pancreas, the tumor was present at the time of CDD but was not detected. Further details of these nine patients are shown in Table 7.

The remaining 13 patients in whom CDD was done for a benign disease recovered uneventfully and the CDD relieved their symptoms; however they died of unrelated causes before 5 years had elapsed from the time of the CDD. Further details of these patients are shown in Table 8.

TABLE 6. *Eight Patients Lost to Follow-up*

Patient	Age (years)	Sex	Hospital	Last Seen After CDD (days)	Condition
1	60	M	V.A.	24	Good
2	58	M	V.A.	30	Good
3	75	M	V.A.	7	Good
4	74	M	V.A.	60	Good
5	48	M	V.A.	12	Good
6	68	M	V.A.	30	Good
7	59	M	U.A.B.	150	Good
8	71	M	U.A.B.	8	Good

All recovered satisfactorily from choledochoduodenostomy and in the short follow-up period the goals of the operation appeared to have been obtained.

CDD, choledochoduodenostomy.
VA, Veterans Administration hospital in Birmingham.
UAB, University of Alabama at Birmingham Hospital.

Number of Surgeons Performing the Choledochoduodenostomies

There were 10 surgeons who performed the 134 choledochoduodenostomies reported herein; however 93.25% of these cases were performed by only four surgeons. The two senior authors of this study performed 78.25% of these 134 cases. The same four surgeons performed 94.4% of them, and the same two surgeons operated in 86% of the 71 cases followed for 5 or more years.

Discussion

The historical development of CDD was summarized by Madden and associates[21] in 1970. The first published experience with CDD by an American surgeon was by R. L. Sanders from Memphis, Tennessee, a member of the Southern Surgical Association from 1921 to 1964. He presented his work in the 57th Annual Meeting of this Association in December 1945. His paper was published in the *Annals of Surgery* in 1946.[22] He described his experience with side-to-side CDD in 25 patients. Nineteen of them had benign obstructive lesions and six had malignant obstructive lesions; only two of his patients died (8%). He noted that 15 patients were living and well many months after the operation. He commented on the effectiveness of CDD to relieve distal obstruction of the CBD and the importance of having a largely dilated CBD as a requirement for good long-term results with CDD.

Despite these favorable results, there was no great enthusiasm in the United States for CDD; the only two large series published in the subsequent 20 years by American surgeons were by Schwartz, Benshimol, and Hurwitz in 1959[23] and by Madden and associates in 1965.[24] In 1967

TABLE 7. *Nine Patients with Initial Diagnosis of Benign Disease, but Subsequently at the Time of Death Were Found to Have a Carcinoma*

Patient	Age (years)	Sex	Initial Diagnosis	Cause of Death	Survival Period After CDD (months)
1	63	M	CBD lithiasis	Cholangiocarcinoma*	29
2	70	M	CP	Lung metast./unknown prim.	12
3	60	M	CP	Ampullary Ca*	24
4	76	M	CBD lithiasis	Ca. pancreas and metast.*	36
5	60	M	CP	Ca. pancreas and metast.*	14
6	79	M	CBD lithiasis	Prostate carcinoma	14
7	54	F	CP	Colon carcinoma	48
8	53	M	CP	Ca. pancreas and metast.*	6
9	52	F	CP	Ca. pancreas and metast.*	13

* Six patients could have had their carcinoma at the time of choledochoduodenostomy (CDD), but it was not detected.

CP, chronic pancreatitis; Ca, carcinoma; Metast, metastases.

Hurwitz and Degenshein published a reappraisal article[25] in which they explained the technical details that determine the success of side-to-side CDD. It should be stated that after the pioneering work of Sanders, Madden[21,24] and Hurwitz[23,25] have been the most avid American advocates of CDD and the wider use of this operation in the United States is due, to a great extent, to their excellent results and persistent enthusiasm for CDD.

The European literature in the past three decades contains a number of publications,[26-34] and a recent report from Latin America[35] carefully evaluates the results, indications, advantages, complications, and shortcomings of CDD; the general consensus is that choledochoduodenostomy is a very satisfactory surgical procedure to treat a variety of obstructing lesions of the distal CBD. Most of these authors stipulate that the diameter of the CBD used for constructing the CDD should be dilated and measure at least 15 mm.

Subsequent to the publications of Madden[21,24] and Hurwitz,[23,25] some American surgeons began to analyze and publish their experience with CDD. Thomas and associates[36] in 1971 and a group from the Cleveland Clinic[37,38] published their experience in the early 1970s; they concluded that CDD had a favorable role to play in various conditions obstructing the CBD. Degenshein et al.,[39] who continued the work of Alfred Hurwitz with CDD in the Maimonides Medical Center in New York, published in 1974 their analysis of their 18-year experience with 175 consecutive CDDs and concluded that it was a safe and effective operation for varied indications. This author was one of the first to show data to prove that the major objection held by some surgeons against CDD, mainly ascending infection from reflux of duodenal contents into the biliary tree, causing recurrent cholangitis, was not a problem as long as the diameter of the CBD used to construct the CDD measured at least 16 mm.

TABLE 8. *Late Deaths After CDD for Nonmalignant Disease*

Patient	Age (years)	Sex	Initial Diagnosis	Cause of Death	Survival After CDD (months)
1	38	M	CP	Subdural hematoma	53
2	81	M	CP	Stroke	12
3	48	M	CP	Unknown	24
4	53	F	CP	Unknown	48
5	87	M	CBD lithiasis	Stroke	24
6	87	M	CBD lithiasis	Heart failure	10
7	46	M	CP	Myocardial infarct	58
8	33	F	CBD lithiasis	Peritonitis and liver abscess	24
9	58	M	CBD lithiasis	Myocardial infarct	24
10	56	F	CBD lithiasis and CP	Nonrelated abdominal surgery and sepsis	8
11	84	M	CBD lithiasis	Heart failure	24
12	85	M	CBD lithiasis	Myocardial infarct	20
13	65	F	CP	Upper GI bleeding	20
					$\bar{x}$ 26 ± 1.5 SEM

CDD, choledochoduodenostomy; CP, chronic pancreatitis; GI, gastrointestinal.

±SEM, standard error of the mean.

Rutledge[40] also reported favorable results using CDD to treat patients with benign biliary obstruction. Gliedman and associates[41] in 1978 published their favorable experiences with CDD, but more importantly emphasized this operation as an adjunct to choledocholithotomy to prevent recurrent choledocholithiasis.

From the results obtained in most of the references quoted above, it can be stated that in 1990 choledochoduodenostomy is an established operation to treat successfully a variety of obstructive lesions of the distal biliary system. Furthermore, under the appropriate circumstances, it is a realistic and perhaps even a better option for closing the CBD, either primary or over a T tube, after choledocholithotomy. The morbidity and mortality rates when CDD is done for the proper indications, when the diameter of the CBD used measures 16 mm or more, and the technical precautions (mobilization of the duodenum, vertical incision in the CBD, and meticulous and precise suture techniques) have been followed, have been better or comparable to other alternative operative methods.

Because of concern about long-term results in patients with CDD, particularly with reference to the occurrence of cholangitis and of the 'sump syndrome,' the prevalent thinking among most surgeons has been that CDD should be performed only in elderly patients and that it should be avoided in younger patients who have a life expectancy of 10 or more years.

The principal aim of this study was to analyze the results obtained with CDD in patients followed for 5 or more years and to determine the safety of this operation in patients who have life expectancies of 15 or more years after CDD. Only two previous communications[12,20] describe the results obtained with CDD on a long-term basis; however, when analyzed closely, the details of how long these patients were followed are limited. Only 26 patients were followed 5 or more years in the series of Cuschieri and associates,[12] and there is no reference to patients followed 10 or more years. The other report by Baker, Neoptolemos, and others,[20] a group with vast experience with CDD, presents a detailed and thorough study of 190 patients who underwent CDD. In this series there were 10 postoperative deaths (5.3%) and 35 late deaths (18%) (9 to 48 months). Of the remaining 145 patients, 114 could be closely followed; the subjective evaluation was that 88% of the 125 patients followed for an unspecified 'long-term period' obtained significant benefits from their CDDs. Five of these patients required a second operation to correct a sump syndrome.[42] Recurrent CBD stones were found in three of these nine patients.

The present investigation followed 71 patients for at least 5 years; 38 of them (53.5%) were followed from 5 to 9 years; 25 (35.3%) from 10 to 14 years, and 8 (11.2%) for 15 or more years, with a total average follow-up of 12.1 ± 1.2 years SEM. This experience suggests that when performed electively in the absence of infection in the sub-hepatic space or unresectable malignant neoplasms, CDD can be performed successfully with a minimal mortality rate (less than 1%).

The analysis of the short-term survivors of this study also suggests that choledochoduodenostomy was remarkably free of complications. A distressing finding, however, was that nine patients thought to have benign non-neoplastic disease at the time of CDD eventually died from malignant disease, clearly pointing out the difficulty in excluding the possibility of the presence of a carcinoma in patients with biliary obstruction due to chronic fibrous pancreatitis. The fact that in some of these patients the carcinoma was not obvious until many months after CDD suggests that carcinoma coexists in patients with chronic pancreatitis, particularly those who develop biliary obstruction.

It is worth noting that of the 40 patients in whom cholecystectomy was performed at the same time as CDD, only 23 (58%) had choledocholithiasis; but in all 40 patients, stenosis of the ampulla was recorded, suggesting that ampullary stenosis may play an important role in symptomatic biliary tract disease with or without choledocholithiasis, particularly after the gallbladder has been removed.

The morbidity of CDD observed in this study (28%) as well as the type of observed complications parallels those previously reported in the literature. Perhaps the most important aspect of this study is the low incidence of cholangitis observed in the 71 patients followed for 5 or more years ($\bar{x}$ 12.1 ± 1.3 years, SEM). The fact that the majority of the cases reported in this study were operated on by two surgeons suggests that experience with CDD improves the results. There were no cases of recurrent choledocholithiasis in this series and none of the patients had symptoms suggesting the presence of the so called 'sump syndrome.'

The review of the pertinent literature and the observations of the present study suggest that the indications for CDD remain very much the same as those detailed by Degenshein[39] in 1974. These indications are detailed below.

Multiple Stones: Multiple stones removed from the CBD with the concomitant uncertainty if all the calculi have been removed, even with the assistance of a postexploratory cholangiogram, usually through a T tube is one indication.

Ampullary Stenosis: Ampullary stenosis, as defined by the inability to pass a calibrated dilator of 3 mm or more in diameter, probably sets up the circumstances for the subsequent development of recurrent choledocholithiasis or a variety of symptoms related to this partial obstruction to the flow of bile into the duodenum. Choledochoduodenostomy appears to offer a definitive solution to these problems, as well as the elimination of recurrent choledocholithiasis, as was the case in this series. When the surgeon is unable to pass the dilator into the duodenum and the intraoperative cholangiogram shows little or no flow of the dye into the duodenum, the possibility of an impacted stone at or near the ampulla, or in a duodenal diverticulum in the same area is real. Despite a number of maneuvers, it is difficult to determine with certainty if this is truly an impacted stone or just ampullary stenosis. Persistence in removing the impacted stone or passing a dilator into the duodenum are blind maneuvers that have a high risk of producing a 'false passage' perforation of the wall of the intrapancreatic portion of the CBD or of traumatizing the pancreas, which can lead to severe acute pancreatitis. Under such circumstances, particularly in the presence of a dilated CBD, a CDD is a definitive, safe, and completely satisfactory solution to these problems.

Pancreatocholangiopathy: Obstruction of the distal CBD by chronic fibrous pancreatitis is a difficult problem that can be resolved by CDD. It must be noted that the elimination of the possibility of carcinoma being a coexisting cause of the obstruction is not possible, and in this study nine patients who at the time of CDD were thought to have nonmalignant obstruction subsequently died of carcinoma.

Malignant Neoplasms: Obstruction of the intrapancreatic CBD by malignant neoplasms that can originate in the ductal epithelium of the pancreas, the mucosa of the CBD, the ampulla, or the duodenum near the ampulla, and that are not resectable, can be palliated effectively with a CDD. However, in many instances, the rapid growth of these tumors results in subsequent obstruction of the CDD or even the displaced duodenum; thus CDD in these circumstances should be performed only when other types of palliative decompression, which would use a segment of the biliary tree further away from the tumor and that do not require mobilization of the duodenum, cannot be done.

Postoperative Biliary Stricture: Unfortunately we still see these types of problems, although it appears to be much less frequent. In most of the cases, when the injury is not discovered at the time it occurs, the distal CBD becomes unsuitable for use in the reconstruction.[43] The alternatives, depending on the anatomic determinants, are reconstruction by anastomosis of the CHBD or the CBD to the duodenum, or to a defunctionalized loop (Roux-Y) of jejunum. When a CDD is constructed, good long-term results can be achieved, as was the case in eight patients in this series.

Avoiding Use of T Tubes: Finally another indication not widely accepted as yet is to construct a CDD when a CBD that measures more than 16 mm in diameter has been explored and one or more of the previously noted indications are not always present, but the conventional methods of closing the choledochotomy over a T tube or primarily are not desirable. Some theoretical disadvantages to using T tubes[44] and even less satisfactory results[45] have been reported. It is somewhat of a 'surgical paradox' to close a choledochotomy with great precision and then 6 to 10 days later blindly pull out the T tube, which probably disrupts the closure, although it is undeniable that thousands of cases treated this way have had a very low incidence of complications. To many surgeons, including ourselves, the construction of a CDD avoids this 'surgical paradox,' obviates the need for the use of a T tube, and nearly eliminates the risk of recurrent or residual choledocholithiasis. Therefore it appears to be logical to offer CDD as a very good alternative to the use of T tubes in patients with dilated CBDs.

The two most notable objections to CDD, the possibility of cholangitis[46–48] and the presence of the symptoms produced by the so called 'sump syndrome,'[4,47,48] occur almost always in instances in which the CDD was constructed for the wrong indications, or when the CBD of these patients measured less than 16 mm in diameter, resulting in a CDD that measures less than 14 mm in length. The long-term observations of this study objectively disprove these objections to CDD as long as the proper precautions are observed. Analysis similar to this study of an adequate number of patients followed from 5 to 15 years after transduodenal sphincteroplasty or transendosopic papillotomy will be required to determine whether those procedures offer similar or better results than those obtained with CDD. Such studies are notably absent from the current literature.

From the observations made in this study, the following inferences can be made: CDD produces good long-term results in the treatment of non-neoplastic obstructing lesions of the distal common bile duct. The size of the CBD is of critical importance in obtaining good long-term results. The diameter of the CBD should be at least 16 mm to allow the construction of a CDD that measures at least 14 mm in length. Meticulous and precise suturing techniques are essential. Intrabiliary stents are not necessary under these circumstances. Extensive technical experience in performing CDD is also an important consideration in assuring good results. If these precautions are observed, cholangitis and symptoms related to the 'sump syndrome' do not occur, or occur very infrequently. In the absence of local sepsis and under elective circumstances, CDD can be performed with very low rates of morbidity and mortality.

Because of the documented good results we have obtained in the patients reported herein followed for 5 to 15 or more years ($\bar{x}$ 12.1 ± 1.3 years, SEM), the notion that CDD should be reserved only for elderly patients with limited (less than 10 years) life expectancy should be revised, and much younger patients who have a longer life expectancy should be considered as viable candidates for CDD under appropriate circumstances.

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DISCUSSIONS

DR. COLIN G. THOMAS, JR., (Chapel Hill, North Carolina): First, with the appropriate indications and technical proficiency, the long-term results of this operation are very good with a negligible incidence of cholangitis or sump syndrome.

Because cholangitis is usually an expression of stasis and bacterial colonization of the biliary tree, we must conclude that this operation effectively drains the biliary tree. The absence of recurrent choledocholithiasis in this series also attests to the absence of bile stasis, which in the presence of *Escherichia coli* and the production of beta glucuronidase converts soluble bilirubin diglucuronide to glucoronic acid and insoluble bilirubin, promoting the formation of sodium bilirubinate calculi.

Second, in some patients on whom the procedure was performed for duct obstruction with a diagnosis of chronic pancreatitis, there was an 11% incidence of pancreatic carcinoma.

We encountered a similar problem when we reported in 1971 our experience with 110 patients undergoing either choledochoduodenostomy or transduodenal sphincteroplasty for presumed benign obstruction of the common duct. Our overall incidence was 5%. This remains a serious challenge and deserves further study.

Third, in their hands under elective circumstances and with the absence of infection in the subhepatic area or an incurable malignant neoplasm, the operation can be done with a mortality rate of less than 1%. This is comparable to the reported mortality rate following endoscopic sphincterotomy and removal of common duct calculi.

There are also some points that should be considered contentious and raise some questions.

What is the evidence that a side-to-side anastomosis is superior to an end-to-side anastomosis? We preferred the latter in our previous report with a transverse division of two thirds of the circumference of the common duct immediately above the duodenum.

Of 52 patients followed for a mean of 3 years, no patient required reoperation because of stones, pancreatitis, or jaundice. One patient with a stone impacted in the ampulla had one attack of discomfort and mild cholangitis at 3 years.

What is the evidence that a duct must be larger than 16 mm in diameter and the constructed choledochoduodenostomy 14 mm or more? This is approximately three times the diameter of a normal common duct, which, according to the 1930 edition of Gray's Anatomy, is the size of a goose quill. For those of you who have not seen a goose quill recently, I have one for an example.

In the event that Dr. Aldrete has had no personal experience with a goose quill, he should be delighted to know that the most recent edition of Gray's Anatomy states the diameter of the common duct is that of a soda straw, with which he has great familiarity.

Probably the most critical point is that the length of anastomosis is at least equivalent to the diameter of the dilated duct. This could be nicely accomplished by a two-thirds transverse section of the common duct in an end-side anastomosis.

Is there an indication for complete transection of the common duct, oversewing the distal end and an end-to-side choledochoduodenostomy? We have had two patients with a normal-sized common duct in whom this procedure was carried out: a patient with an intrapancreatic choledochal cyst and associated pain and a 14-year-old boy with calcification in the head of the pancreas and pain. Both patients have remained free of discomfort with no evidence of common bile duct obstruction.

This slide illustrates another technique of an end-to-side choledochoduodenostomy, which we carried out in a 1971 study, and it required minimal mobilization of the duodenum. And, of course, the wider the duct, the easier it is to perform.

How has the availability of endoscopic sphincterotomy with or without extraction of biliary calculi influence the indications for choledochoduodenostomy?

DR. JOHN L. SAWYERS (Nashville, Tennessee): This is an important paper because of the length of follow-up in a large series of patients who have undergone choledochoduodenostomy. There are very few reports in which the follow-up is a minimum of 5 years for all patients and extends to more than 15 years for several patients.

It has generally been my preference to use a Roux-en-Y choledochojejunostomy in preference to a choledochoduodenostomy because of a few patients who developed cholangitis after choledochoduodenostomy and two patients who required operation for the sump syndrome.

I was surprised that Dr. Aldrete has had no patients who have had the sump syndrome and that only 4.2% percent of his patients developed cholangitis in the postoperative period. We would concur with him that these good results are probably related to careful construction of the anastomosis. The authors emphasize the importance of anastomosis of at least 16 mm in diameter.

I remember being on a panel with Dr. Gliedman, who forcefully and repeatedly emphasized that choledochoduodenostomy should be at least 2.5 cm in diameter, and he held up his thumb, which he alleged to measure exactly one inch to illustrate that point.

Now we believe that choledochoduodenostomy should not be used for patients who have malignant disease. Would Dr. Andrete agree that Roux-en-Y choledochojejunostomy is preferable to bypass distant malignant obstruction?

We have encountered patients with chronic pancreatitis severe enough to make mobilization or kocherization of the duodenum difficult. Certainly in these cases Roux-en-Y choledochojejunostomy is technically easier than choledochoduodenostomy.

How do you perform biliary enteric anastomosis? Do you use a one-layer monofilament material or a two-layer suture anastomosis? Are the sutures interrupted or continuous? Is 16 mm the minimum diameter or should the anastomosis be larger, if possible?

Dr. Aldrete indicates that choledochoduodenostomy offers a definitive solution to the problem of ampullary stenosis. We have usually preferred transduodenal sphincteroplasty for these patients because this gives us an opportunity to observe and biopsy the sphincter. When does Dr. Aldrete use sphincteroplasty?

Dr. M. J. Fischer recently described two patients with hepatic abscess due to *E. coli* after a choledochoduodenostomy. The author, Dr. Fischer, thought this may have occurred because the anastomosis was too small. Have you, Dr. Aldrete, encountered this complication?

DR. ROBERT HERMANN (Cleveland, Ohio): We have used choledochoduodenostomy frequently at the Cleveland Clinic for the past 25 to 30 years, for the same indications as outlined by Dr. Aldrete, because it is a safe and effective procedure if the bile duct is dilated.

Choledochoduodenostomy provides a direct anastomosis between bile duct and duodenum, which I believe is physiologically superior to a choledochojejunostomy.

If the anastomosis is made low in the bile duct so a long sump segment cannot occur below the anastomosis and is made generously large, as other authors have emphasized—and we make ours about 2 cm long—then stenosis of the anastomosis with recurrent cholangitis will not occur.

Another advantage of choledochoduodenostomy not mentioned by the authors is that endoscopists can easily cannulate or endoscope and follow this anastomosis by gastroduodenoscopy.

Here you see the view through an endoscope at the time of a duodenoscopy. You can easily diagnose and treat recurrent problems with this method.

In 1981 Dr. David Vogt and I reviewed a comparative series of patients who had had either choledochoduodenostomy, choledochojejunostomy using a Roux-en-Y technique, or transduodenal sphincteroplasty to treat a variety of benign and malignant biliary and pancreatic problems. We found that all three operations were effective and gave equivalent results. The long-term results related more to the disease being treated than to the operative procedure chosen.

Choledochoduodenostomy stood the test of time in our study as well, with 86% excellent or good results and 7% fair results. Two per cent of our patients had recurrent cholangitis, and in each case it was due to a poorly constructed anastomosis.

Choledochoduodenostomy is a good operative procedure for young patients as well as older ones and is equal to all the other methods of biliary reconstruction.

DR. PHILIP SANDBLOM (Lausanne, Switzerland): The reason I rise is, first, to express my gratitude to the Southern Surgical Association for many years of membership and many, wonderful congresses. This is one of the nicest that I attend.

The second is because I think I owe it to Dr. Aldrete as I have always campaigned against choledochoduodenostomy mostly because of the risk for ascending cholangitis.

When I presented a paper on this about 30 years ago, the risk for cholangitis was much higher than was presented today — between 20% and 30%. The risk for stenosis of the anastomosis also was larger. There is a great tendency for those anastomoses to constrict. The modern technique evidently reduces this risk of stenosis very much.

The only way of really knowing the exact number is to identify the cases in which there were autopsies, and it is hard to collect that kind of information.

We found about 20 patients who had died and been autopsied more than 5 years after the operation. To our surprise nearly all of them had pathologic signs of cholangitis, in some cases even multiple liver abscesses in which the history had not given any sign of cholangitis. We must thus expect that many of those cases of choledochoduodenostomy have cholangitis without frank symptoms.

It is not very healthy to go around with multiple liver abscesses despite absence of symptoms, so I still would advocate the choledochojejunostomy to al Roux-en-Y loop.

DR. JOAQUIN S. ALDRETE (Closing discussion): To address the question posed by Dr. Thomas, whether the anastomoses should be side-to-side or end-to-side, most of our cases had a side-to-side choledochoduodenostomy placed, as described by Dr. Herman, as low as possible in the common bile duct. When doing the choledochotomy, one must anticipate the possible need for doing a choledochoduodenostomy; therefore placing the choledochotomy is very important.

I think the two techniques are good. There may be slight differences. Perhaps it is somewhat faster to do the side-to-side procedure. In doing the end-to-side, one must transect the bile duct, and nowadays, because of the experience with liver transplantation, a not uncommon anatomic variation of a right hepatic artery that originates from the superior mesenteric artery and runs on the right side of the common bile duct has been recognized. Sometimes this artery is small and if one is not aware of this variation, this artery can be easily included in the ligature that occludes the distal end of the transected bile duct. Ligating this hepatic artery is innocuous. It can result in an hepatic abscess.

Why the size? Well I'm trying to play it safe, Tim. I said 16 mm. As time went on, we have gotten better and now we can construct a 12-mm or 13-mm anastomosis by using very precise suturing techniques, but it is safer to do it with a common bile duct that measures 16 mm or more.

Regarding the length of the choledochodenostomy, you lose about 2 mm if you do an end-to-side or a side-to-side procedure from the diameter of the common bile duct. It does not matter if you make it very long. Still the bile will run only through the diameter of the common bile duct.

How endoscopic sphincterotomy or sphincteroplasty will change the indications, only time will tell. I hope that the results presented today will be used as the parameter to measure the results with those newer operations.

My friend Dr. Sawyers always has the appropriate comments and is always very kind to us. I completely agree that in the presence of a malignant tumor, it is probably better to use a Roux-en-Y using the jejunum because the choledochoduodenostomy usually ends up right next to the tumor. And by doing a choledochojejunostomy, one can be further away from the tumor. I also agree that in any situation in which it is difficult to mobilize the duodenum, choledochojejunostomy should be performed.

As for the details of the technique, we mobilize the duodenum extensively. We make a vertical or slightly slanted incision in the lowest portion of the common bile duct that measures a few more millimeters of the diameter or the bile duct. And then we very precisely construct an anastomosis with 5.0 Prolene, sometimes in one layer, but if at all possible, we place an outer layer of interrupted silk sutures that do not penetrate the mucosa. I like to use 4.0 or 5.0 silks that come with a very small needle, usually used in neurosurgery. In addition the exposure should be very good and the extensive mobilization of the duodenum allows an anastomosis without any tension. Under these circumstances, this operation is fun to do and the expected results are quite good.

I think Dr. Hermann has been a pioneer, as has been Dr. Thomas, with this operation. His comments are those of an authority in the field, and I am delighted that he agrees with our findings, that his experience parallels ours.

Dr. Sandblom, I appreciate very much your comments. I believe that the recognition and preservation of this anomalous right hepatic artery, eliminates the risk of the hepatic abscesses.

We saw a few patients who had a choledochoduodenostomy for many years and had an autopsy. You always can see a change in the epithelium of the bile duct, but I do not think you can call that cholangitis. The diagnosis of cholangitis is when the patient has fever, chills, and must receive antibiotics.

But, indeed, when you look at the biliary side of a choledochoduodenostomy there are some changes from the normal epithelium. It is not a normal connection, but it is better than an obstructed common bile duct.

The Economic Burden of Gallstone Lithotripsy

Will Cost Determine Its Fate?

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Gallstone lithotripsy (LITHO) was performed on 52 patients who underwent 107 procedures. Two hundred sixty-seven gallstone patients were screened and 215 (81%) were excluded. Excessive stone burden and nonvisualization by oral cholecystogram (OCG) were the most common reasons for exclusion. The hospital course of 100 excluded patients who later underwent elective cholecystectomy was evaluated for length of hospital stay (2.3 days) and total cost of treatment ($3685.00). Successful fragmentation to less than 5 mm was achieved in 43 LITHO patients (83%). Five LITHO patients (10%) required conversion to operative management. Complications of LITHO included acute cholecystitis (1 of 52 patients) and biliary colic (17 of 52 patients, or 33%). Multiple procedures in one patient were common. Costs for LITHO were calculated in two ways: first the individual cost for each of the 52 candidates; second the cost for successful LITHO was calculated by excluding five patients who required operation as well as five patients (10%) who are predicted failures of LITHO. Including the preoperative evaluation, treatment, recovery room, and follow-up, the individual LITHO cost for 52 patients was $8275.00. If the same total expenditure is calculated after excluding patients who required operation and those predicted to fail, the cost per 'successful' LITHO procedure was $10,245. The cost of 1 year of bile acid therapy is $1949.00 or $2413.00 per 'successful' procedure. Follow-up costs were $1232.00 per patient or $1525.00 per 'successful' procedure. The added LITHO cost incurred by screening eventual noncandidates was $904.00 per successful procedure. The sum of these individual costs was $15,087.00 per success, as compared to $3685.00 for cholecystectomy. No allowance was made for cost of stone recurrence. Lithotripsy costs appear to be sufficiently high to render the procedure unlikely to emerge as the treatment of choice.

GALLSTONES HAVE BEEN managed successfully by means of an operative cholecystectomy throughout most of this century. Although the operation is now remarkably safe (0.2% to 0.4% mortality rate)[1] and the procedure is permanently curative, several recent technologic advances have been applied to the treatment of gallstones in attempts to avert the morbidity of operation and to diminish the great cost of an estimated 500,000 cholecystectomies per year in the United States. Extracorporeal shock wave lithotripsy (LITHO) was first applied to kidney stones and later evaluated for the treatment of gallstones.[2,3] An early communication from Munich reported that 80% of patients were stone free after 1 year.[3] The process of selection excluded 75% of gallstone patients from the study,[3] and this limitation of the application of LITHO has been consistent in subsequent reports.[4–6] Unfortunately early high rates of success have not been reproduced.[4,7] Even in patients with stones that represent the most favorable situation for LITHO (a solitary stone measuring less than 20 mm in diameter), later reports[4,8] have had rates of stone eradication that compare poorly with the early Munich experience.[2,3] Multiple procedures are required routinely.[4–8]

The concept that the effectiveness of gallstone lithotripsy might be enhanced by dissolution of remaining stone fragments arose from the experience of the National Cooperative Gallstone Study, in which bile acid therapy was most effective in stones measuring less than 5 mm in diameter.[9,10] All lithotripsy programs have combined LITHO fragmentation (to less than 5 mm) with later bile-acid therapy.[1–8]

Lithotripsy devices generally cost almost $1,000,000. This cost and the need for multiple lithotripsy procedures has raised the need for cost–benefit analysis. One study compared a single LITHO procedure to elective cholecystectomy (EC) and found the costs to be comparable, although LITHO costs were higher.[11] The costs of bile

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acid treatment and follow-up were not considered in this study. We evaluated the total cost of successful LITHO therapy and compared it to costs of EC.

Material and Methods

Each LITHO patient was a participant in a trial approved by the Institutional Review Board (IRB) of the University of Texas Medical Branch at Galveston (IRB 89-124). The trial was a part of a multicenter, Federal Drug Administration-approved Investigational Device Exemption investigation and informed consent was obtained in all cases. All studies were performed using the Lithostar,(R) plus Biliary Lithotriptor (Siemens, Islip, NY); this unit uses an electromagnetic shock source. The original design of the Lithostar(R) trial consisted of two randomized groups. One group received a 14-day course of bile acid therapy (ursodeoxycholic acid [Actigall; Ciba-Geigy Corp., Summitt, NJ] 10 mg/kg/day) before LITHO treatment. In the second group, bile acid therapy commenced on the day of LITHO treatment. All participants remained on bile acids until 3 months after being found to be stone free or until 18 months after LITHO if dissolution therapy was deemed a failure. Each procedure was performed in an outpatient setting after an overnight fast. The patients received light intravenous sedation (diazepam and meperidine). Each procedure was limited to 4000 shocks over a range of energy settings.

The two most common reasons for exclusion from the study were nonvisualization of the gallbladder after oral cholecystogram (OCG), and excessive stone burden (that is, cumulative stone diameters greater than 3 cm × 3 cm [9 cm^2] in two dimensions as measured by ultrasonogram). Other less common exclusion criteria are listed in Table 1. A LITHO procedure was considered successful when all stones were fragmented to a diameter of less than 5 mm. Repeat LITHO procedures were scheduled when fragmentation was not successful.

After initiation of our study, all patients with gallstones who were referred to our surgery clinic were screened as potential candidates for LITHO. Excessive stone burden was sufficient to exclude candidates. All patients with a stone burden of less than 9 cm^2 had OCG. Nonvisualization was followed by HIDA scan. All candidates for LITHO then required preprocedure laboratory studies. Individual LITHO costs included the following: diagnostic ultrasonogram (USG, \$145.00), OCG (\$186.00), HIDA scan (\$373.00) when necessary, lab studies (\$127.00), outpatient operating room charge, professional fee, recovery room (\$201.00), and bile acid therapy.

Although some patients were free of stones in less than 1 year after LITHO and some patients crossed over to operative management in less than 1 year, it is clear from our experience and that of others[4–8] that most LITHO patients require more than 1 year of bile acid therapy to achieve stone dissolution. For that reason, in calculating costs, we estimated 1 year of bile acid therapy for each LITHO patient. Individual LITHO costs were first calculated for each of the 52 LITHO candidates. To determine the cost of a successful LITHO patient, we removed the five patients who required operation (n = 47) and we made the modest estimate of a 10% failure rate (5 of 52 patients) and excluded them. This resulted in an estimated 42 successful LITHO patients.

Because a large number of eventual operative candidates underwent what proved to be unnecessary OCG or HIDA exams, the cost of these tests were applied to the cost of a 'successful' LITHO patient. Thus the sum of all LITHO costs plus the cost of 1 year of bile acid therapy plus the cost of screening tests for noncandidates were divided by the total number of LITHO candidates (n = 52), and also by the estimated number of 'successful' LITHO patients (n = 42). No attempt was made to assign costs for the likely event of stone recurrence.

We assessed no professional fees for this study by previous arrangement. We estimated a fee of \$1250.00 per procedure. Operating room costs for LITHO were established as \$2860.00 for a first procedure, \$1430.00 for a second, \$2860.00 for a third, \$1430.00 for a fourth, and so on.

We evaluated 100 patients with gallstones who were screened and excluded as candidates for LITHO and who later underwent EC. Their length of hospitalization and their total cost of treatment were analyzed. Total EC costs included diagnostic USG, clinic visit, operating room, professional fee, anesthesia, recovery room, hospital room, and laboratory tests.

Actual costs are listed in Table 2. The actual hospital bill for each patient was added to pre- and postoperative costs for all 100 patients and this sum was divided by 100 to arrive at cost per patient. This cost was compared to the cost per LITHO patient and to the cost per 'successful' LITHO patient.

TABLE 1. *Exclusion Criteria for Gallstone Lithotripsy Program*

Excessive stone burden (>9 cm^2)
Nonvisualization by oral cholecystogram
Lung tissue in shock path
Calcified blood vessels in shock path
Pregnancy
Bleeding diathesis
Acute cholecystitis

Results

We screened 267 gallstone patients and performed lithotripsy on 52 patients (19% yield). We should note that we were intent on entering patients into the study; no one who qualified was excluded. Among the remaining

TABLE 2. *Itemized Cost of Services and Procedures for Elective Cholecystectomy (EC) and for Gallstone Lithotripsy (LITHO)*

Lab tests	$59	$127
Central supply	$161	—
Pharmacy	$77	—
X-ray	$112	—
Operating room	$714	$2860/$1430
Recovery room	$201	—
OR anesthesia supplies	$199	—
Hospital room @ $260.00/day	$520	—
Professional fee	$1591	$1250
Total/procedure	$3634	$4438

215 patients, 201 underwent EC (14 patients chose to delay treatment). We randomly selected 100 of these 201 patients and compared them to the 52 LITHO patients. The EC group had 72 women and 28 men with a mean age of 41 years (range, 19 to 69 years). Lithotripsy was composed of 42 women and 10 men with a mean age of 37 years (range, 21 to 66 years). Sixty-two EC patients were Mexican-American as were 29 LITHO patients. The groups are starting at LITHO.

Elective Cholecystectomy

The mean length of hospitalization for patients who underwent EC was 2.3 days. Twenty-seven patients were discharged on the first day after operation. There were no deaths. The sum of all charges incurred by EC patients was $368,500. Individual cost per patient were assessed as $3685.00. This charge encompassed all pre-, intra-, and postoperative care and professional fees.

Gallstone Lithotripsy

Fifty-two patients underwent 107 LITHO procedures. Successful fragmentation of stones (measuring less than 5 mm) was achieved in 43 patients (83%). Five patients dropped out of the LITHO program and had an operation, one for acute cholecystitis, and four for intractable symptoms of biliary colic. Four patients had fragments larger than 5 mm after four LITHO procedures and no subsequent attempts were made to fragment stones. In all patients the mean stone burden was 5.5 ± 0.7 cm^2 and mean stone number was 4.1 ± 0.8. Only seven patients had single stones measuring less than 20 mm. Four of those seven patients are stone free. Twelve patients are stone free after a mean follow-up of 11.4 months (23% stone free). The mean stone burden in the stone-free patients was 1.7 ± 0.5 cm^2, and the mean stone number was 1.6 ± 0.4.

Complications of lithotripsy included skin erythema in 43 patients, reversible benign ventricular ectopy in 8 patients (15%), microscopic hematuria in 2 patients (4%), biliary colic in 17 (33%), acute cholecystitis in 1 (2%). No patients developed pancreatitis. One patient had 5 LITHO procedures, 4 patients had 4, 14 had 3, 13 had 2, and 18 had 1 procedure. No complications of Actigall therapy were noted. Thirty-one patients have had more than 1 year follow-up.

Lithotripsy Costs

Professional fees for LITHO were not charged to these patients because of study arrangements, but we estimated them to be $1250.00. The total cost of all LITHO procedures, work-up, and recovery room was $430,291.00. This represents an average individual cost of $8275.00 for 52 patients. By excluding the estimated 10% failure rate (5 patients) and the 5 patients who required operation, the mean cost of 'successful' lithotripsy in 42 patients was $10,245.00 per patient.

Actigall Costs

Actigall (10 mg/kg/day) costs $5.34 per day ($1949.00 per year). This cost in 52 patients represented $101,348.00. As a cost per 42 'successful' LITHO patients, bile acid therapy was calculated as $2413.00 per patient.

Additional Costs

One year of follow-up for LITHO included a clinic visit ($36.00) every 3 months in which lab tests ($127.00) and USG ($145.00) were performed at each. This represented a yearly cost of $1232.00 or $64,064.00 for 52 patients. The cost for 42 'successful' LITHO patients was $1525.00 per patient.

To recruit 52 LITHO patients it was necessary to screen 267 gallstone patients. Among the 215 excluded patients, otherwise unnecessary OCGs ($186.00) were obtained in 146 patients and otherwise unnecessary HIDA scans ($373.00) were performed on 29 patients. This was calculated as a total cost of $37,973.00 and as a cost of $904.00 per 'successful' LITHO patient.

The cost of lithotripsy treatment for gallstones, expressed as cost per successful LITHO patient, is shown in Table 3. Combined individual costs of the LITHO procedure ($10,245.00), bile acid therapy ($2413.00), follow-up ($1525.00), and screen ($904.00) was $15,087.00, as compared to EC costs of $3685.00.

Discussion

Even though operative cholecystectomy in the treatment of gallstones has the dual advantage of being curative and safe,[1] much recent attention has been focused on nonoperative measures to treat gallstones. The main stated goals of this attention are to avoid the morbidity of operation and to diminish costs (which have been estimated to be as high as $2 billion per year in the United States). In early reports from Munich,[7,2,3] extracorporeal shock

TABLE 3. *Calculated Cost for Elective Cholecystectomy (EC), for 52 Gallstone Lithotripsy Patients (LITHO) and for 42 Successful Lithotripsy Patients ('Successful Litho')*

Procedure	Procedure	Bile Acid	Follow-up	Screen	Total
EC	$3549	—	$136	—	$3685
LITHO (n:52)	$8275	$1949	$1232	S730	$12,186
'Successful LITHO' (n:42)	$10,245	$2413	$1525	S904	$15,087

Bile acid therapy is cost for 1 year, follow-up cost for LITHO is at 3-month intervals for 1 year and screen costs reflect the cost of screening gallstone patients who were eventually excluded.

wave lithotripsy of gallstones appeared to be highly effective in a subset of gallstone patients who had functioning gallbladders and small stone burdens, especially when combined with bile acid therapy. The high success rates reported in the initial trials have not been reproduced in later reports,[4–7] but criteria for entrance into trials have been liberalized. Our current study, for example, did not limit the number of stones and permitted treatment when a rim of calcium was seen by radiograph, a feature that served to exclude patients in previous studies.[1–8]

Although a variety of shock sources have been developed,[2,4,8] one unifying characteristic of each of these machines has been their very high cost, often $1 million. Perhaps for this reason, most estimates of the hospital charges for these procedures have been in the range of $3000.00 to $4000.00 per procedure (similar charges are now accepted for renal lithotripsy). The question of the potential economic burden of gallstone lithotripsy, if it were applied to even a fraction of the 500,000 patients yearly who undergo operative cholecystectomy in the United States, has not yet been addressed fully. Our calculated cost of $3685.00 per patient for cholecystectomy is comparable to previous reports but also reflects the reduction in hospital costs resulting from shortened hospital stays. In one recent study,[11] the total cost for EC was $6240.00, compared to $8100.00 for LITHO. Patients in that study remained hospitalized for more than 4 days after operation and their LITHO charges represented a single treatment and failed to include costs of bile acid therapy.

We included a number of costs to a LITHO patient that have not been included conventionally. Even without these additions, the comparative costs of the two procedure are $3685.00 for EC and $8275.00 for LITHO. We think it is reasonable to add the cost of bile acid therapy. This agent is costly ($1949.00 per year for an unknown numbers of years; we have added the cost for only 1 year). Cross-over to operation has been observed in all trials.[2–6] Similarly treatment failure has been a feature of all reports with incidences as high as 67%[4] in certain subsets of gallstone patients. Our estimated rate of treatment failure (10%) is modest because the most favorable results yet reported have achieved stone-free rates of 90% at 1 year.[3] Thus we have defined 'successful' LITHO patients by excluding five patients who underwent operation and five who failed treatment. Finally the costs of evaluating 80% of all gallstone patients who are screened for LITHO and excluded must be considered. Our 19% yield of LITHO candidates is consistent with all previous reports.[2–7] Although the cost of an OCG is not high, the number of OCG exams could become very large if lithotripsy programs were widely instituted. On consideration we think these additions to cost estimates for LITHO are valid. Using these calculations, the cost of EC ($3685.00) is certainly much lower than that of LITHO ($15,087.00). Only if cut to one quarter of their current rate would LITHO charges approximate those of EC.

The extent of risk of gallstone recurrence first became clear in follow-up studies of the National Cooperative Gallstone Study.[9] Recurrence rates of about 10% per year were recorded in the first 5 years after termination of treatment.[10] Thistle[12] suggested that gallstone recurrence is a benign event and that such stones are almost always asymptomatic.[12] Rates of recurrence of gallstones after gallstone lithotripsy are similar to those found after bile salt dissolution therapy.[13] This study[13] failed to confirm the suggestion[12] that recurrent stones tended to be 'silent stones' but instead reported significant symptoms in patients in whom gallstones recurred. Even so we have not chosen to add any estimated cost of gallstone recurrence to the cost of a lithotripsy program, although, if lithotripsy were widely applied for long periods, recurrent stones might prove to be the most costly aspect of the program.

Several more elaborate additions to routine gallstone lithotripsy have been proposed. Because gallstone dissolution with bile acids is effective only for cholesterol gallstones, efforts have been directed at lithotripsy of pigmented gallstones. Routine use of computed tomography scans of the gallbladder to detect microcalcifications in pigmented stones has been suggested.[14] Peine and colleagues[15] advocated combining gallstone lithotripsy with direct dissolution therapy (methyl-tert-butylether) by means of perfusion of methyl-tert-butylether into the gallbladder *via* a percutaneous cholecystostomy tube (with the patient under general anesthesia) in the treatment of partially calcified gallstones.[15] The potential added costs of such additional modes of diagnosis and therapy could be great.

Finally the recent development of techniques whereby operative cholecystectomy can be performed with a laparoscope has further simplified EC.[16] Not only have the lengths of hospital stay been reduced, but postoperative convalescence and days absent from work have been significantly reduced. At this point in the evolution of treatment of gallstones, the development of a highly successful laparoscopic method would appear to establish operative cholecystectomy as the treatment of choice for all who qualify. Patients who do not qualify for laparoscopic operation (some patients with acute cholecystitis or previous upper abdominal operations, interalia) could be treated by open cholecystectomy.

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DISCUSSIONS

DR. R. SCOTT JONES (Charlottesville, Virginia): The data look quite clear. In addition to the cost, we also need to look at other items in terms of efficacy and also a comparison of the fact that when one undergoes cholecystectomy, the gallbladder is, by definition, gone. And when the lithotripsy is completed, the gallbladder remains in place, which is also a serious consideration.

But all of these things have been examined, at one time or another. And I simply would like to make a comment, particularly about lithotripsy. And the comment is that lithotripsy, at least in the United States, is presently and will, for the foreseeable future, be done on an experimental or trial basis.

All patients now included in lithotripsy treatment are entered under a protocol that defines the patient population. The number of shocks applied are defined by protocol. The intensity of the shock is defined by protocol, and the mechanism for follow-up and the tests and evaluation also are done by protocol. In other words it is fairly rigid.

I think it is probable that when the FDA sees fit to liberalize or accept lithotripsy that we will learn a lot more about it than we now know. We will be able to increase the intensity of the shocks and increase the frequency and also modify the protocol in such a way as to reduce costs considerably.

So now we do not know where we stand with lithotripsy, and it appears highly unlikely that it will be released, at least for another 3 years, so it would probably be another 5 years before we really have an opportunity to work on this.

Having said that, though, I think Dr. Thompson's points are all good. And that for lithotripsy to emerge as an effective therapy, it will certainly have to improve considerably in terms of efficacy, and we will have to do a lot to decrease the cost.

DR. LES WILLIAMS (Nashville, Tennessee): Jim has already suggested the answer to one of my two questions. We at Vanderbilt are in a biliary lithotripsy study. The piezoelectric machine was developed at Vanderbilt, and we have analyzed 106 patients who have been treated.

We have looked at our finances a little differently and also because our protocol happens not to involve bile salts, we don't have the constant bile salts, but we are treating cholesterol-calcified stones, so we have a constant CT. There are, thus, minor differences.

But we looked at the original data. And using the protocol requirements, the cost of lithotripsy for 1 year was exactly the same as the cost of elective traditional hospitalized cholecystectomy.

So that those data suggest the same. And, indeed, we had one patient of five eligible for treatment, just as they did.

However, if you look at those, as we did, most of those costs are laboratory driven. And they are driven by the FDA protocol because of safety.

Having now done a number of these, I believe we would not, in routine practice, continue those costs. So in that context, the cost would be decreased. However we had one other difference. Of the eligible patients to be treated with lithotripsy even at the beginning, because we lived in Nashville, the home of the laparoscopic cholecystectomy enthusiasm before the rest of the world joined it, we had only two of three patients who would elect lithotripsy.

Recently in 6 months we have had a single patient willing to have lithotripsy, and she had a morbid fear of anesthesia, and that was the only reason. So we can not find anybody to treat with lithotripsy.

Therefore my questions are two. Is it not laparoscopic cholecystectomy that will negate lithotripsy as a meaningful treatment of gallstones?

And, in fact, if lithotripsy is to have a place, would it not be for what the FDA protocols do not now permit, the treatment of a patient who is a severe anesthetic risk, treatment of a patient whose gallstones are unusual, that is, after TPN, rapid weight loss, that is, those circumstances in which the *in situ* gallbladder may not necessarily be the source of recurrent gallstones?

DR. RON JONES (Dallas, Texas): Dr. Thompson again questions the role of biliary lithotripsy in the management of patients with cholelithiasis.

The first patient treated in the United States under an FDA-approved protocol at an ID site was at Baylor Hospital in Dallas in January 1988, approximately 3 years ago. And that was a patient of Dr. David Vanderpool, who happens to be a guest at this meeting, and that patient was treated with a Medstone machine.

We treated 94 patients with 135 treatments, for a retreatment rate of 35% to 40%. Our results at Baylor Hospital are almost identical to those reported in the *New England Journal of Medicine* a few weeks ago, which summarized the Dornier data.

There are more than 65 investigational sites in the United States studying this technology. The best results are in patients with stones that are in a subset with 1.5 cm or less without calcification. And there you can obtain up to a 50% stone-free rate.

Nevertheless, because of the small group of patients who qualify for this treatment, the fact that the stone-free rate is not very good, even in these patients, and because laparoscopic cholecystectomy has become so popular, Medstone International closed all protocols approximately 1 month ago and announced that they were not going to pursue for a period of time the development of biliary lithotripsy and would now concentrate only on renal lithotripsy.

Therefore it is questionable whether biliary lithotripsy will have a significant role in the future in the management of patients with biliary tract disease.

Dr. W. H. Nealon (Closing discussion): It seems not to be a very controversial issue that we are presenting today.

I would comment that the data that Dr. Williams presented concerning the use of the piezo electric machine for lithotripsy and the fact that their costs were identical in 1 year, perhaps is important information, although they do not appear to have added to their calculations all ancillary costs. And certainly you are right that some of the protocol requirements for laboratory studies do increase the cost.

However it is important to know that repeat ultrasound, which, of course, is never indicated in a patient who has had a cholecystectomy, is one that you would need to anticipate in any patient who has been treated by a measure that leaves the gallbladder *in situ.* And, of course, the global view of knowing the gallbladder will remain and that gallstone recurrence is likely in at least one half of those patients makes that kind of repeat analysis likely.

The question of whether laparoscopic cholecystectomy is not really the issue is important. Knowing that laparoscopic techniques have been available for years, it is an interesting quirk of history that both of these technologies should be applied to the treatment of gallstones almost simultaneously.

But you are absolutely right. Our ability to recruit patients for lithotripsy has decreased considerably since the introduction of laparoscopic cholecystectomy. Most patient referrals come with a request for laparoscopic cholecystectomy.

I think you may be right that some of the severe-risk patients would be candidates for this procedure, although the fact that in general cholesterol gallstones are the indication, things such as TPN-induced gallstones, which are primarily pigmented stones, would not be candidates for this procedure anyway.

I was aware of Medstone's withdrawal from the whole world of biliary lithotripsy, and that is, by itself, enough of a comment on what the likely future of biliary lithotripsy can be.

Open *Versus* Laparoscopic Cholecystectomy

A Comparison of Postoperative Pulmonary Function

RICHARD C. FRAZEE, M.D.,* JOHN W. ROBERTS, M.D.,* GYMAN C. OKESON, M.D.,† RICHARD E. SYMMONDS, M.D.,*
SAMUEL K. SNYDER, M.D.,* JOHN C. HENDRICKS, M.D.,* and RANDALL W. SMITH, M.D.*

Upper abdominal surgery is associated with characteristic changes in pulmonary function which increase the risk of lower lobe atelectasis. Sixteen patients undergoing open cholecystectomy and 20 patients undergoing laparoscopic cholecystectomy were prospectively evaluated by pulmonary function tests (forced vital capacity [FVC], forced expiratory volume [FEV-1], and forced expiratory flow [FEF] 25% to 75%) before operation and on the morning after surgery to determine if the laparoscopic technique lessens the pulmonary risk. Fraction of the baseline pulmonary function was calculated by dividing the postoperative pulmonary function by the preoperative pulmonary function and multiplying by 100%. Postoperative FVC measured 52% of preoperative function for open cholecystectomy and 73% for laparoscopic cholecystectomy ($p = 0.002$). Postoperative FEV-1 measured 53% of baseline function for open cholecystectomy and 72% for laparoscopic cholecystectomy ($p = 0.006$). Postoperative FEF 25% to 75% measured 53% for open cholecystectomy and 81% for laparoscopic cholecystectomy ($p = 0.07$). It is concluded that laparoscopic cholecystectomy offers improved pulmonary function compared to the open technique.

LAPAROSCOPIC CHOLECYSTECTOMY HAS been used in several medical centers in the United States in the past 2 years. The advantages of the laparoscopic technique include less patient discomfort, shorter hospitalization, and shorter interval to return to full activities after operation.[1] It has been postulated that due to the minimal incisional discomfort, postoperative pulmonary function following laparoscopic cholecystectomy would be improved as compared to open cholecystectomy. This study prospectively evaluated this hypothesis in patients undergoing elective cholecystectomy.

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Materials and Methods

A prospective evaluation of all patients undergoing either open or laparoscopic cholecystectomy during a 6-week period from May 1, 1990 through June 15, 1990 was performed. Patients undergoing concomitant common duct exploration were excluded from the study. This time period coincided with a stage early in our experience with laparoscopic cholecystectomy when one half of our surgeons were performing laparoscopic cholecystectomy and one half were not. New patients with symptomatic cholelithiasis were assigned randomly to individual staff surgeons, as is our customary practice, with no attempt to preselect patients into one operative procedure or the other. All patients were counseled before operation on routine postoperative pulmonary care, including use of the incentive spirometer.

Pulmonary function testing was performed before operation in all patients in the pulmonary lab using the Sensomedic 2800™ body plethysmography and flow volume loop. Forced vital capacity (FVC), forced expiratory volume at 1 second (FEV-1), and forced expiratory flow at 25% to 75% (FEF 25%–75%) were obtained. Bronchodilators were not administered during the testing. Absolute and percentage predicted values were measured.

The morning after surgery all patients underwent bedside pulmonary function using the Puritan Bennet PS 600™ processing spirometer, again measuring FEV-1, FVC, and FEF 25%–75%. Patient analgesia was individualized to meet each patient's requirements. This ranged from no analgesia to systemic narcotics.

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A fraction of the baseline pulmonary function was calculated by dividing postoperative pulmonary function by the preoperative pulmonary function and multiplying by 100%. Statistical analysis was performed using the t test.

Results

During the 6-week study period, 16 patients underwent open and 20 patients underwent laparoscopic cholecystectomy. The indication for surgery in all patients was chronic symptomatic cholelithiasis. There were no cases of acute cholecystitis. There were 15 women and 1 man undergoing open cholecystectomy, with a mean age of 54 years (range, 21 to 86 years). Sixty-two per cent had a history of smoking more than one-half pack per day. There were 18 women and 2 man having laparoscopic cholecystectomy with a mean age of 47 years (range, 23 to 84 years). One half had a history of smoking more than one-half pack per day. No patient in either group was on chronic bronchodilator therapy (Table 1).

All surgeries were performed using general anesthesia. Open cholecystectomy was performed through a standard subcostal incision. Laparoscopic cholecystectomy was performed using a four trocar technique. Carbon dioxide was insufflated intraperitoneally during laparoscopic cholecystectomy with intra-abdominal pressures maintained at 20 mm mercury. Mean length of surgery was 70 minutes (range, 40 to 160 minutes) for open cholecystectomy and 87 minutes for laparoscopic cholecystectomy ($p = 0.18$). Mean duration of anesthesia was 114 minutes (range, 75 to 215 minutes) for open cholecystectomy and 129 minutes (range, 80 to 170 minutes) for laparoscopic cholecystectomy ($p = 0.20$).

Postoperative FVC measured 52% of preoperative function for open cholecystectomy and 74% for laparoscopic cholecystectomy ($p = 0.002$). Postoperative FEV-1 measured 53% for baseline function for open cholecystectomy and 72% for laparoscopic cholecystectomy ($p = 0.006$). Postoperative FEF 25%–75% measured 53% for preoperative functioning for open cholecystectomy and 81% for laparoscopic cholecystectomy ($p = 0.07$) (Table 2).

Discussion

The pulmonary effects of surgery and general anesthesia have been well documented. Impaired gas exchange occurs with the induction of general anesthesia and can be related to the effects of general anesthesia on distribution of ventilation, lung and chest wall mechanics, lung volumes, shunt fraction, and ventilation perfusion relationships.[2,3] Patient position, type of inhaled anesthetic, tidal volume, and airway pressure during general anesthesia can influence gas exchange and lung mechanics.[4,5]

TABLE 1. *Patient Demographics*

Demographic	Open	Laparoscopic
Number	16	20
M:F	1:15	2:18
Mean age (years)	54 (21–86)	47 (23–84)
Smoking Hx	62%	50%

Hx, history.

TABLE 2. *Fraction of Baseline Pulmonary Function*

Function	Open (%)	Laparoscopic (%)	p Value
FVC	54	73	$p = 0.002$
FEV_1	52	72	$p = 0.006$
$FEF_{25\%-75\%}$	53	81	$p = 0.07$

Upper abdominal surgery can produce dysfunctional pulmonary mechanics independent of the effects of general anesthesia. Characteristically a restrictive pattern is seen with reductions in vital capacity and functional residual capacity (FRC).[6–8] After upper abdominal surgery, vital capacity may decrease by 50% or more, while functional residual capacity and tidal volume are reduced by 30%. Forced expiratory volume in one second will show similar postoperative decreases.[9] Latimer[8] demonstrated that this decrease in FEV-1 is secondary to a loss of lung volume rather than a major airway obstruction. The majority of patients undergoing extremity surgery using general anesthesia do not experience a similar decrease in FRC. Therefore this postoperative abnormality cannot be attributed to the effects of the anesthetic alone.[7,10]

The etiology of the pulmonary dysfunction after upper abdominal surgery is understood incompletely and multiple factors may contribute. Incisional pain produces a pattern of shallow inspiration to minimize discomfort. Functionally the chest and abdominal walls are interdependent during respiration. The increase in intra-abdominal pressure with expansion of the chest wall causes outward movement of the abdominal wall.[11] Incisional pain will restrict this outward movement. Relief of pain by epidural analgesia or intercostal block only partially restores vital capacity and FRC toward preoperative values. This indicates that upper abdominal incisions interfere with the ability to expand the thorax independent of pain factors alone.

Diaphragmatic dysfunction also plays a role in impaired ventilation. During normal respiration, 60% of the inspired tidal volume is contributed by a contraction of the diaphragm.[12] After upper abdominal surgery, diaphragmatic excursion is decreased[13] and paradoxical motion of the diaphragm can occur,[14] which leads to increased demand on intercostal muscle contribution to respiration. This change can cause a decrease in the functional residual capacity.

The postoperative changes in pulmonary function improve gradually but are still demonstrable in most patients 5 to 7 days after surgery.[8,15] These changes become clinically significant when they contribute to pathologic conditions such as atelectasis, hypoxemia, and pneumonia.

The location and type of abdominal incision has been shown repeatedly to play a role in postoperative ventilatory impairment.[9,16–18] Laparoscopic cholecystectomy requires minimal muscle disruption and produces less postoperative pain. Because of these factors, it has been postulated that postoperative pulmonary dysfunction would be diminished. These benefits may be offset, however, by longer operating and anesthetic time required for laparoscopic cholecystectomy as well as pulmonary problems associated with the pneumoperitoneum performed during the procedure. The current study addressed this question in 26 patients. The three pulmonary functions tested (FVC, FEV-1, and FEF 25%–75%) all demonstrated approximately 20% to 25% better function in the patients undergoing laparoscopic cholecystectomy compared to the patients undergoing open cholecystectomy. These differences were present despite longer anesthetic and operative times for the laparoscopic cholecystectomy group. The physiologic alterations associated with upper abdominal surgery are reduced significantly with the laparoscopic technique. The advantages demonstrated by pulmonary function testing should translate clinically into better gas exchange, improved functional residual capacity, and better lung volume. This improvement in pulmonary function may translate into a lower incidence of respiratory complications.

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DISCUSSIONS

DR. HENRY LAWS (Birmingham, Alabama): In Dr. DeBakey's elegant presidential address he emphasized the two major advances that have made surgery as we know it possible: anesthesia in the United States and antisepsis in Europe. I would like to go a little further with this.

The major advances in the latter half of the 20th century, in my judgment, include the development of the pump oxygenator, intravenous nutrition, fiberoptics, video control operations, and transplantation.

I was privileged to hear Drs. Rhoads, Dudrich, Vars, and Wilmore present their paper on intravenous nutrition at this meeting at this hotel in 1968. Video-controlled surgery is changing and will dramatically alter surgery as we know it, not just cholecystectomy.

I would like to comment primarily on paper number 32, and I would like to thank Drs. Roberts and Frazee for sending me a copy of their manuscript.

The authors report a simple but crisp study of a major parameter of postoperative change, that of pulmonary function. Dr. Roberts and colleagues found, as have others, that significant features of pulmonary function are decreased by approximately 50% in the immediate postoperative period by subcostal incision. They have demonstrated that laparoscopic cholecystectomy does impair function significantly less than does open cholecystectomy. As a matter of fact, the decrease was only about 25% with laparoscopic cholecystectomy, as opposed to 50% with open cholecystectomy.

I have several questions for these authors. Your time of operation with laparoscopic cholecystectomy was a little longer. Now that you have more experience with that operation, does it equal that of open cholecystectomy?

You note in your manuscript that you use a four-portal technique. We use a five-portal McKernan technique, one for the light source, two for each hand of the surgeon, and one for each hand of the assistant. Do you use two ports for the surgeon or two ports for the assistant?

Have you now studied more patients with pre-existing pulmonary dysfunction as opposed to those with relatively normal pulmonary function and determined the amount of additional impairment by open as opposed to laparoscopic cholecystectomy?

Considering patients with COPD, do you intend to change the criteria you might use to proffer operation, that is, by the laparoscope as opposed to the open operation that you were doing last year?

It pleased me to note that you used the open technique for your initial entry. Because 85% of our patients have had a previous abdominal operation, indeed, several have had at least two previous laparoscopic procedures, we think that should be done in every instance. Is that what you do?

DR. RICHARD C. FRAZEE (Closing discussion): It is rare that an advance in a surgical procedure produces such a dramatic improvement in postoperative recovery as we have seen with laparoscopic cholecystectomy. I am impressed with the similarities between our study and the subsequent two studies and many of the discussants.

I would like to address some of the questions specific to our study and then some of the other questions addressed to the other papers, about which we differ slightly with the other authors.

Dr. Laws you asked about our time of operation. Indeed it has decreased with further experience. This procedure is very learner dependent. The more experience you gain with the procedure, the easier and more facile you become with the instruments. And, in fact, our average operating time for cholecystectomy alone now averages between 45 and 60 minutes. Including operative cholangiography, the time increases by an additional 20 minutes.

You asked about our four-trochar technique. This is a technique we began from the beginning, involving a periumbilical cutdown procedure. The three additional trochars are placed in the subcostal position.

The scope is inserted through the periumbilical position and usually is operated by a medical student at our institution because we are a teaching institution. The remaining three trochars are shared between the operating surgeon and his assistant. One is used for liver retraction, a second for retraction of the gallbladder, and a third for the actual dissection. The operating surgeon operates the dissecting trochar independently while the other two are held by the assistant.

You asked if our criteria for patient selection has changed, and indeed it has. And this has come about by instruction of our internal medicine colleagues. By presenting our data to them, we are now seeing patients who had not been referred for surgery on the basis of pulmonary function. We are now seeing patients with borderline pulmonary function who are considered a relative contraindication to general surgery now coming for laparoscopic surgery and doing quite well.

Dr. Meyers your series is very impressive, but I am concerned by the number of common bile duct injuries in your series. We have now performed close to 200 laparoscopic cholecystectomies with no common duct injuries, and I think there is no reason that with adequate training and caution in this procedure the experience with common duct injury with a laparoscopic procedure should be no higher than with open cholecystectomy.

Dr. Voyles you posed several questions regarding cost containment and I applaud you for those. We fall into your category of the group of surgeons who started with electrocautery and have not abandoned that. When establishing this procedure at our institution, we thought we wanted to make it as similar to the open procedure as we could, rather than trying to learn new techniques. So we started initially with the electrocautery for dissection and have found no indication to change that procedure.

I would question one of the benefits of the disposable trochars that we have found, namely that the seal that is available for down-sizing the trochar from a 10-mm trochar to a 5-mm trochar allows less loss of pneumoperitoneum during dissection. This may be one of the advantages of the disposable trochars.

You talked about the use of routine operative cholangiography. Again this was something we wanted to make similar to our experience with open cholecystectomy. There are a number of series that have shown equal results practicing selective cholangiography as opposed to routine cholangiography, and we have taken this stance in our laparoscopic patients as well.

We do not think operative cholangiography is necessary to prevent common bile duct injury or to identify anatomy. Much as in the open procedure, the anatomy should be identified by direct visualization rather than cholangiography.

Dr. Wilson we took a similar approach to your institution in that all six of our general surgeons have subsequently become trained and accredited in the laparoscopic procedure. We frequently assist one another in the more difficult cases, and this combined effort has improved our results.

Dr. Chavez your comments about a mini-laparotomy were shared by one of my partners. He was convinced that through the use of a small right upper quadrant incision that a postoperative recovery would be no different than with a laparoscopic procedure. I am pleased to say he has now been converted to an advocate of laparoscopic cholecystectomy.

Dr. Thompson I agree that the indications for laparoscopic surgery will continue to expand. And right now I am afraid we fall into phase 1 of your different phases. We are still in the enthusiastic phase. I hope we do not fall into the subsequent phase 5.

Appraisal of Laparoscopic Cholecystectomy

HERSCHEL A. GRAVES, JR., M.D., JEANNE F. BALLINGER, M.D., and WILLIAM J. ANDERSON, M.D.

This paper reports the experience of three general surgeons performing 304 laparoscopic cholecystectomies in three private hospitals between October 1989 and November 1990. Laparoscopic cholecystectomy boasts two major advantages over the conventional procedure: the remarkable reduction in postoperative pain and economic benefit, largely due to the patient's early return to work. Revealing a complication rate of 2% and no deaths, this study has shown that this procedure can offer patients these advantages with a medical risk no greater than that accompanying conventional cholecystectomy. Patient safety must be paramount, and it is the responsibility of the surgical community to ensure that all surgeons receive the highest quality training and that the technique is applied appropriately.

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MORE THAN 500,000 PATIENTS undergo traditional open cholecystectomy each year in the United States. While elective cholecystectomy now carries extremely low morbidity and mortality rates, the operation does incur sizable expense in terms of hospitalization and time lost from work. In the past several decades, research has been conducted along several avenues to develop less invasive, painful, and expensive methods of gallstone treatment. Such methods as the application of oral desaturation agents (chenodeoxycholic acid, ursodeoxycholic acid), contact dissolution agents methyl tert-butylene ether (MTBE), and extracorporeal shock wave lithotripsy are limited by stone content, size, and number. In addition they leave intact a gallbladder already known to harbor lithogenic bile. Thus these nonoperative methods are inadequate for a large proportion of gallstone patients and they cannot promise permanent cure from gallstone disease.

While embraced widely by American physicians only during the past two decades, laparoscopy was first described in Europe at the turn of the century.[1] Through the 1930s laparoscopic techniques and instruments to employ them were perfected, although the procedure was then used mostly to diagnose liver disease. Laparoscopy was first reported by Ruddock in the United States in 1933, and until the 1970s it remained largely a diagnostic procedure.[2] During that decade gynecologic surgeons developed laparoscopic tubal ligation, and in the early 1980s, Daniell[3] reported the combined use of laser and laparoscopy for the treatment of endometriosis. These laparoscopic operations produced less postoperative pain, required shorter in-hospital and outpatient recovery times, and allowed rapid return to normal activity.

The application of laparoscopy to general surgical diseases has increased in frequency and effectiveness in the past 5 years. Its use has been proposed to diagnose liver metastases and thus determine operability in pancreatic cancer. The first laparoscopic cholecystectomy was performed in May 1988 by DuBois in France.[4] In June 1988 McKernan and Saye performed a piecemeal cholecystectomy *via* the laparoscope (oral personal communication, October 1990). Reddick and Olsen,[5] however, devised the currently used method for laparoscopic cholecystectomy, performing their first case in September 1988.

Laparoscopic cholecystectomy achieves the goals of shorter recovery time, decreased expense, less postoperative pain, and improved cosmesis. It can be applied to nearly all patients with gallstones and by completely removing the gallbladder, should produce the same long-term results as standard open cholecystectomy. It has spread rapidly through the surgical world but without benefit of carefully controlled prospective studies. Thus we think it is imperative that experience with the procedure be reviewed carefully to ensure that the short-term

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gains mentioned above are not outweighed by increased deaths and long-term losses such as major common duct injuries.

We report our experience, as general surgeons, performing 304 laparoscopic cholecystectomies in three private hospitals between October 1989 and November 1990. We had the advantage of being tutored by Reddick and Olsen, the originators of the procedure.

Materials and Methods

Indications for laparoscopic cholecystectomy are the same as for the open procedure, that being symptomatic cholelithiasis. There were three asymptomatic patients in our series who underwent the closed procedure at the request of the medical service because of associated medical conditions. One patient had asymptomatic chronic myelogenous leukemia and the other two were diabetics, one anticipating pregnancy. The procedure was thought justified to eliminate the specter of possible serious situations should complicating acute cholecystitis occur in the future.

Contraindications

The early contraindications for using laparoscopic cholecystectomy were the presence of large stones, evidence of acute inflammation, common duct stones, or a history of previous abdominal surgery. The admirable cautiousness of those pioneers of the procedure is evidenced by their report of performing 25 minilaparotomy cholecystectomies during the same time frame in which they were proceeding with their first 25 laparoscopic approaches.[5] Experience has lessened the need for these dictums, but throughout the process of refining the procedure others will arise. Large stones can be removed without difficulty. Adhesions from the omentum to the anterior abdominal wall due to previous surgery usually can be taken down. Many acutely inflamed gallbladders can be removed, but each presents an individual decision. Common bile duct stones known to be present before surgery that cannot be removed by endoscopic sphincterotomy argue for an open cholecystectomy with choledocholithotomy. Although pregnancy has not been considered a firm contraindication to laparoscopic procedures by gynecologists, we think an open cholecystectomy is preferable should symptomatic cholelithiasis demand surgical intervention during gestation.

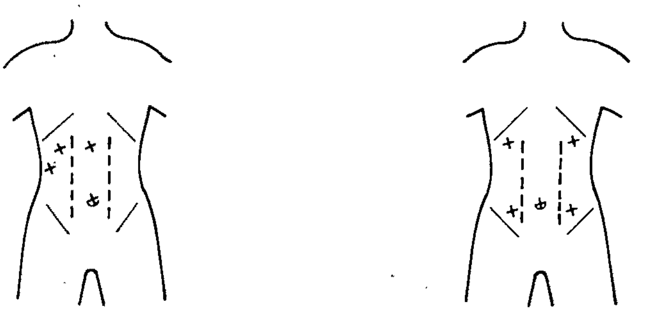
Operative Technique

It should be mentioned at the outset that good functioning equipment and trained personnel knowledgeable in its use and maintenance are of paramount importance in carrying out a laparoscopic surgical program.

General anesthesia was administered to patients throughout this series with no related complications. All patients received a broad spectrum antibiotic during induction of the anesthesia. The operative technique employed uses video monitors and instrumentation through four cannulas introduced by trocars (two 5 mm, one 10 mm, and one 11 mm) into the peritoneal cavity that has been distended by the insufflation of 3 to 4 L carbon dioxide. The insufflation is accomplished by inserting a Veress needle[6] through the umbilicus or one of the four quadrants of the abdomen, varying these locations to avoid possible bowel loops adherent to the anterior abdominal wall from previous surgery (Fig. 1). The initial video camera can locate these possible adhesions, which usually can be removed by dissection from other ports.

A Hasson cannula always can be inserted through the umbilicus to avoid adhesions from previous surgery and allow safe insufflation.[7] It has been used in six patients in this series and has been a significant aid in safely determining the status of intra-abdominal adhesions in the area of previous incisions at the umbilicus. A slightly longer incision, approximately 2 cm, is made in the umbilicus and carried carefully through the linea alba fascia. By blunt dissection with the finger and a clamp, the presence or absence of underlying adhesions or a loop of intestine is determined and, if present, pushed aside to allow finger entry into the free peritoneal cavity. The Hasson cannula then is passed into said cavity and held in place by a 0-polyglactin suture taken in either side of the fascial opening and hooked to the cannula holding it firmly in place, thus preventing the escape of pneumoperitoneum (Fig. 2). Adhesions of the omentum to the anterior abdominal wall usually can be dissected away bluntly or with cautery to allow appropriate cannula insertion and exposure of the gallbladder. Fitzgibbons has used the Hasson cannula in every case, thus avoiding any Veress needle or trochar injury (oral personal communication, October 1990).

Once the cannulas are in place, reverse Trendelenberg position is assumed and the patient tilted to the left.



TROCHAR SITES

INSUFFLATION SITES

FIG. 1. Possible CO^2 insufflation sites (umbilical and right upper quadrant most frequently used) and subsequent trochar sites.

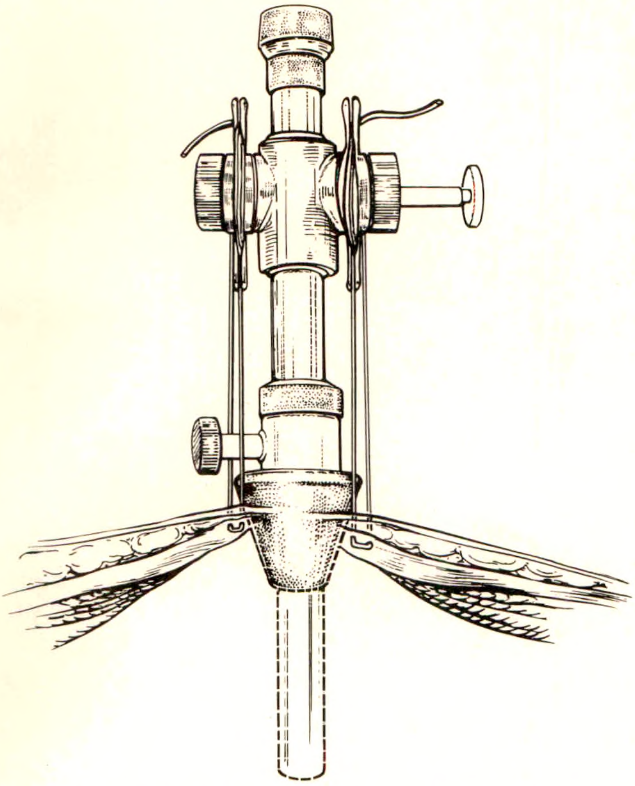


FIG. 2. Hasson cannula with sutures applied to the paraumbilical fascia and hooked to the cannula.

Graspers are then used to retract the fundus of the gallbladder laterally and cephalad and the infundibulum laterally or medially. Appropriate traction is of utmost importance, and if the graspers repeatedly slip from their purchase of a distended gallbladder, partial or complete aspiration is used at will. Acutely inflamed gallbladders are always aspirated.

It is of singular importance that the junction of the gallbladder and the cystic duct be demonstrated accurately. Accordingly dissection should begin by stripping the peritoneum and fat from Hartman's pouch down to and then from the cystic duct. Calot's triangle should not be entered first. The artery then is dissected at this time if available, but this can be delayed if the duct blocks proper visualization. At this point, a cholangiogram can be made by inserting a catheter into the cystic duct just proximal to a clip applied at the junction of the duct with the gallbladder. A catheter is held in place with an Olsen clamp around the cystic duct, and 15 mL of contrast material is injected with all structures in view before graspers are removed. An additional 5 to 10 mL of contrast is injected just before the first of two films is made (Fig. 3).

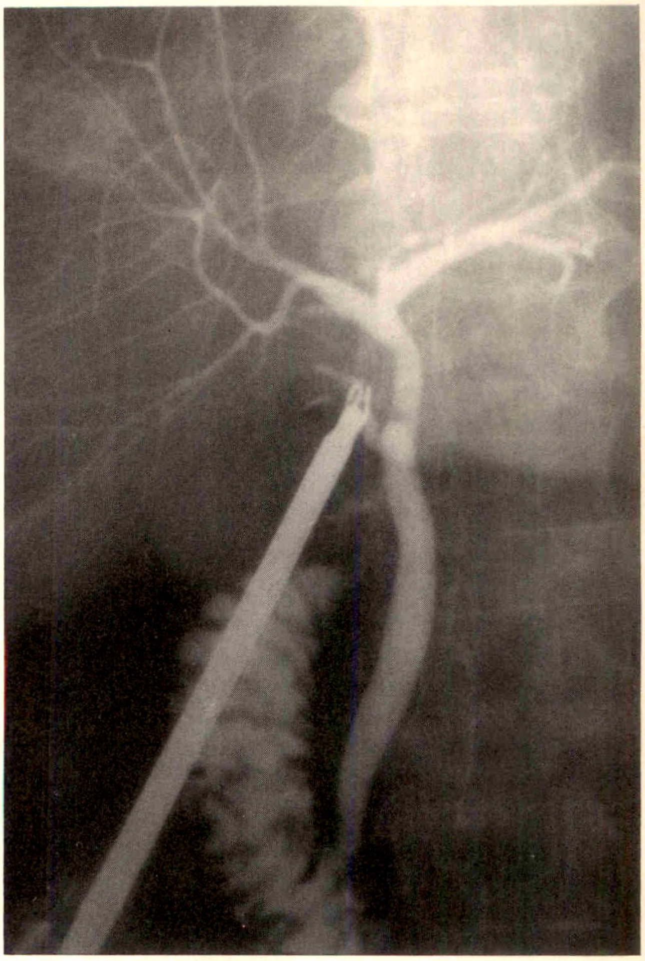


FIG. 3. Normal intraoperative cholangiogram made *via* catheter in cystic duct and held in place by an Olsen clamp.

An alternate cholangiographic method being studied consists of aspirating the bile from the gallbladder and injecting 30 mL of contrast material under C-arm observation. This not only allows evaluation of the common bile duct for stones or blockage but also gives the advantage of outlining the ductal anatomy (Figs. 4 and 5). If universally employed, this technique could reduce greatly the incidence of common bile duct injuries.

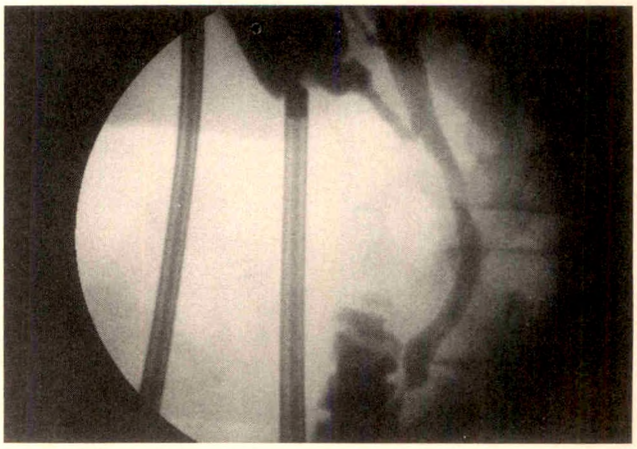


FIG. 4. Normal intraoperative cholangiogram *via* gallbladder with C-arm fluoroscopy.

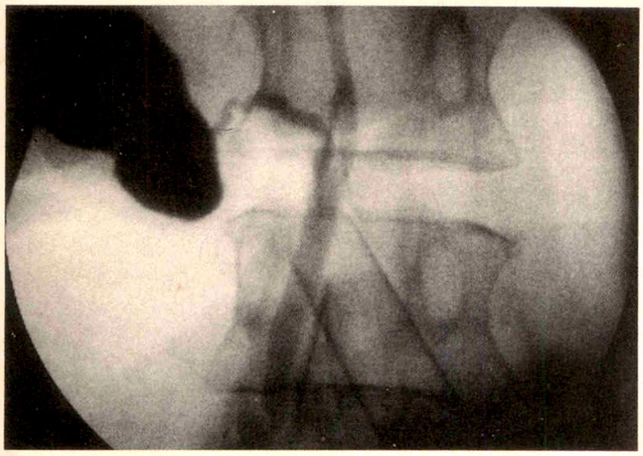


FIG. 5. Intraoperative cholangiogram *via* gallbladder C-arm revealing the cystic duct emptying into the right hepatic duct or an accessory duct.

After applying distal and at least two proximal clips to the cystic duct and artery, they are divided with scissors. The gallbladder is retracted anteriorly and the mesentery between these structures and the liver is dissected for a frequently found additional artery. The gallbladder then is dissected away from the liver with an electrocautery or laser, effecting hemostasis in the process.

Before the gallbladder finally is detached from the liver, the previously dissected liver bed and Calot's triangle area should be inspected carefully for possible bleeding. These areas are difficult to re-examine after the gallbladder has been detached from the liver. If the gallbladder is torn during the dissection, the bile and small stones can be suctioned away and the opening closed with a chromic catgut endoloop. If stones escape, however, they should be recovered as well as possible. With adequate irrigation and suction, we have experienced no complication with the escape of bile and a few stones.

Results

Of the 304 patients in this study, 82% were female, and the ages ranged from 14 to 83 years, with an average of 50 years. Weight ranged from 90 to 312 pounds, with an average weight of 164 pounds (Table 1). Ultrasound was used for diagnosis in 90% of the cases (Table 2). Pathologic examination revealed that 94% had demonstrated stones and the remaining 6% had chronic cholecystitis with or without cholesterolosis or polyps (Table 3). Ten patients (3.3%) had acute cholecystitis, four of whom underwent successful laparoscopic removal (Table 4). Of the 304 attempted laparoscopic procedures, 283 (93.1%) were completed successfully. Conversion to an open procedure was required in 21 patients (6.9%), most often because of difficulty in defining anatomy due to either acute or chronic inflammatory changes (Table 5). The conversion rate varied among the three surgeons, ranging from 1.6% to 4.4% to 12%. This illustrates that surgeons will encounter varying pathologic conditions and must manage each case in the safest possible manner. No conversions were required for uncontrolled bleeding and no subsequent laparotomies were necessary. Operative time ranged from 35 to 216 minutes and averaged 99 minutes. The laser dissection was used in 41% and cautery in 59%. Most cases in the last 4 months of this study were done with the cautery. Cholangiograms were attempted in 170 patients (56%) and successfully completed in 100 patients (Table 6). They were normal in 93% of the studies made. Postoperative endoscopic retrograde cholangiopancreatogram (ERCP) was carried out in five patients in whom intraoperative cholangiogram indicated stones. Regarding this patient group, stones were found and successfully removed by endoscopic sphincterotomy in three patients (Figs. 6 and 7) and no stones were found in two patients. Preoperative ERCP was performed in 11 patients because of suspected common duct stones. No stones were found in eight patients, and stones were found and successfully removed in three patients. It is important to note that in this 16-

TABLE 1. *Laparoscopic Cholecystectomy*

Demographic Data	
Female	82%
Male	18%
Age	14–83 years (avg., 50 years)
Weight	90–312 lbs (avg., 164 lbs)
	29 female patients > 200 lbs
	11 male patients > 200 lbs

TABLE 2. *Diagnosis*

Total Cases	Diagnostic Test
90%	Ultrasound
10%	OCG, CT, HIDA, and/or US
5%	No stones reported

TABLE 3. *Pathology*

Total Cases	Pathology
94%	Cholelithiasis
6%	Chronic cholecystitis (with or without cholesterolosis polyp)
3.3%	Acute cholecystitis (all with stones)

TABLE 4. *Acute Cholecystitis (n = 10)*

Cases	Pathology
6 Converted	3 hydrops
	2 acute and chronic
	1 empyema
4 Removed	1 hydrops
	1 acute hemorrhagic
	2 acute and chronic

TABLE 5. *Conversion to Open*

	No.
Acute cholecystitis	6
Chronic scarring	6
R/o CBD injury	2
Cystic duct stone impaction	2
Obesity	1
Difficult dissection	17
CBD injury	1
Carcinoma gallbladder	1
Benign liver tumor	1
Small intestine injury	1
Conversion to open cholecystostomy	21 (6.9%)

patient group pancreatitis developed in three of these patients and delayed surgery in two.

Complications developed in eight patients (2%), six of whom had prolonged ileus (Table 7). Ileus accounted for all three readmissions to the hospital. No secondary laparotomies were required, and no retained common duct stones have been encountered. The single common duct injury occurred when a cholangiogram was performed through a small common duct. This was recognized on the cholangiogram and successfully managed by repairing the choledochotomy over a size 8 T tube. Anterior traction of the gallbladder can straighten the angle of the cystic and common ducts and cause the surgeon to mistake a small common duct for the cystic duct (Fig. 8). There were no pulmonary complications, infections, or deaths.

Eighty-six per cent of our patients were admitted on the day of surgery, with 75% discharged within 24 hours of surgery and 89% by 48 hours (Table 8). This compares to an average hospital stay of 6.1 days for an open cholecystectomy.[8] The time for return to the patient's occupation averaged 7.35 days, ranging from 2 to 21 days. Examination of hospital costs revealed a savings, which varied at the three institutions, ranging from $1500.00 to essentially the same charges for laparoscopic cholecystectomy when compared to an open, uncomplicated cholecystectomy. The lack of more substantial savings despite shortened hospital stay appears to be related to the current expense of the equipment charges from the operating room.

Unexpected pathology was found in three instances: peritoneal implants from an asymptomatic carcinoma of the pancreas in an 83-year-old woman, carcinoma of the gallbladder in a 43-year-old man, and a benign hepatic tumor in a 40-year-old woman. An associated bilateral oophorectomy was performed on one posthysterectomy patient.

TABLE 6. *Cholangiography*

	Cases
Attempted	170%–56% (total)
Successful	100%–59% (attempted)
Normal	93
Abnormal	7–1 choledochal cyst 1 suspicion CBD injury 5 ? CBD stones

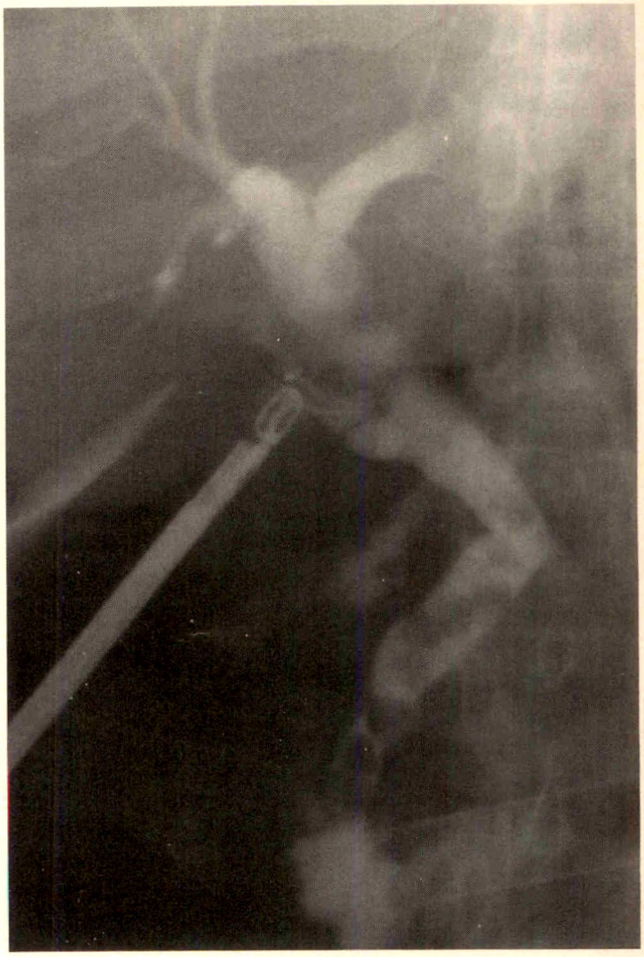


FIG. 6. Intraoperative cholangiogram *via* cystic duct catheter showing multiple common bile duct stones removed 4 days later by endoscopic sphincterotomy–balloon technique.

Discussion

The morbidity and mortality rates of elective conventional cholecystectomy have diminished to extremely low levels in the past several decades. Innovative gallstone treatment should at least match this success rate. This study was undertaken to clarify the benefits of laparoscopic cholecystectomy and to ensure that these are not accompanied by unacceptable medical risk.

Laparoscopic cholecystectomy boasts two major advantages over the conventional procedure. The first is remarkable reduction in postoperative pain, and although seemingly obvious, this has not been quantified. Patients may experience some soreness around the incisions and sometimes right shoulder pain referred from CO^2 and fluid trapped beneath the diaphragm. It has not yet been documented whether this reduction in pain will result in de-

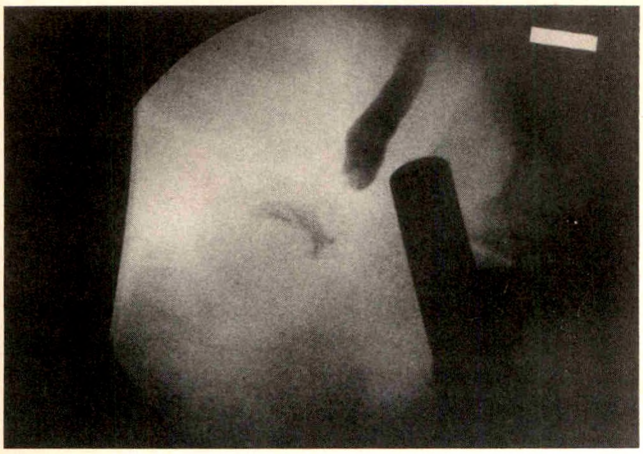


FIG. 7. Intraoperative cholangiogram *via* the gallbladder revealing a stone in ampulla of the common bile duct, removed 4 days later by endoscopic sphincterotomy–balloon technique.

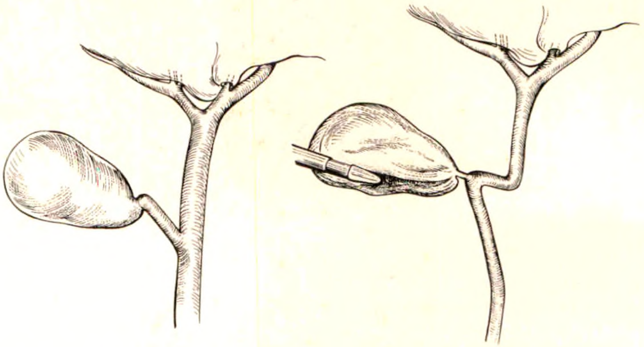


FIG. 8. Sketch illustrating relative normal gallbladder cystic duct–common bile duct relationships and sizes, and how anteriolateral traction of the gallbladder can distort this relationship and make a small common bile duct have the appearance of a cystic duct.

creased pulmonary or cardiac complication rates, but these problems have not been experienced in our series. It is an interesting concept that the pain of a procedure results mostly from the incision and not from visceral dissection.

The second major area of benefit is largely economic. Because the bowel is minimally manipulated, if at all, laparoscopic cholecystectomy results in a smaller incidence of postoperative ileus. This, along with the reduction in pain, allows a shortened hospital stay. While 77% of our patients have remained in the hospital one or two nights, 12% have been allowed, after careful screening, to leave the hospital the evening of the operative day. This compares well to a mean length of stay for conventional cholecystectomy of 6.1 days. This decreased hospitalization has not yet resulted in significantly lower hospital costs because the savings are currently offset by the high cost of the equipment and thus greater charges for its use. These costs may diminish as the equipment becomes more readily available and perhaps less expensive.

The greatest economic benefit of laparoscopic cholecystectomy comes from the rapid return to normal activity that it permits. Most patients are discharged from the hospital without activity restrictions and can return to work as soon as they feel able. Our mean return to work of 7.3 days is certainly superior to the 3 to 6 weeks usually required after the open procedure. Again, while not yet documented, this should result in great personal savings and thus overall societal gain.

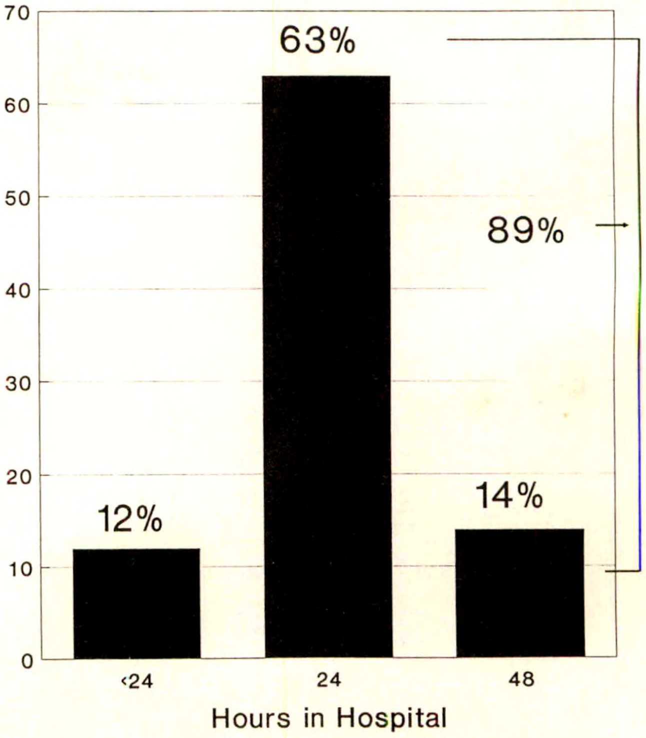
TABLE 7. *Complications*

Complication	No.
Prolonged ileus	6
CBD injury	1
Small bowel injury	1
Death	0
Bleeding	0
Trochar injury	0
Bile leak	0
Abdominal or Wd infection	0
Pulmonary	0
Total	8 (2.0%)

CBD, common bile duct, Wd, wound.

Are these benefits outweighed by undue surgical risk? From our experience, we think the answer is no. In our series we found only six episodes of ileus, three significant postoperative fevers, and one small bowel injury that occurred during dissection of an abdominal wall adhesion. One minor common bile duct injury occurred that was recognized and immediately repaired at the initial oper-

TABLE 8



ation without sequelae. We had no episodes of significant bleeding and none of our patients required reoperation. In those instances of conversion to an open procedure, we did not consider the conversion either a complication or a failure because in each instance this course was chosen by the operating surgeon as the safest for the patient. This emphasis on patient safety above all else may in part be responsible for our relatively low complication rate.

Accompanying the explosive adoption of laparoscopic cholecystectomy have been many anecdotes about unrecognized common bile duct injury, severe bleeding, and even death. Such anecdotes make it imperative that all surgeons honestly collect and review their results and that all surgeons performing the procedure be thoroughly trained and strictly credentialed. All staff surgeons at our three hospitals are certified by the American Board of Surgery. The hospitals' credentialing committees currently require the following: completion of accredited courses in laparoscopy and laser (if laser is to be used) and a preceptorship with a trained laparoscopic surgeon on at least 10 patients, with the applicant as operating surgeon in three. While these criteria are fairly easy to satisfy in a medical center where there are many trained surgeons, they are much more difficult to meet in areas where the technique is not yet practiced. A realistic solution to the problem of training has not yet been identified but is one that the surgical community must address if the procedure is to succeed for the public good.[9-11]

We have used both laser and cautery in the past but now have converted almost entirely to the cautery because it is more hemostatic, less expensive, and may be safer for the patient. We found no difference in postoperative recovery that would support the exclusive use of the modality.

Intraoperative cholangiography can be carried out in most patients undergoing laparoscopic cholecystectomy. It may evolve that it can be performed in all patients, except those with cystic duct obstruction, when the gallbladder injection with C-arm use is used. The indications for performing the study in the laparoscopic setting should be the same as for open cholecystectomy, and this is varied from specific clinical and anatomic criteria to its routine use in all patients.[12,13] Although the incidence may be small, we have encountered two patients with common duct stones without clinical history or laboratory findings suggestive of their presence (Figs. 6 and 7). The value of outlining the ductal anatomy is another strong reason for its routine use in the laparoscopic setting. Fitzgibbons advises its use in all cases of acute cholecystitis to confirm ductal position (oral personal communication, November 1990).

The need for preoperative ERCP in patients suspected of having a common bile duct stone should be evaluated carefully. There should be objective evidence by laboratory findings, ultrasonography, or radionuclear scan. If the indication is questionable, we favor waiting for an intraoperative cholangiogram confirmation. If this study indicates common bile duct stones, a postoperative endoscopic sphincterotomy then can be used. Although the incidence is low, ERCP carries a distinct risk of complication and should not be used at will.

Despite the rapid recovery and great patient satisfaction with this method of gallbladder removal, we emphasize that the indication for operation should remain symptomatic cholelithiasis. The initial contraindications to the procedure (acute cholecystitis, intra-abdominal adhesions, and suspected common duct disease) became more relative as our experience increased. While these conditions do make the procedure more difficult, they can be managed safely through the laparoscope along with patience and judgment. It may be advisable for the learning surgeon to avoid laparoscopic procedures in patients with increased technical risk until his or her experience grows, or to operate on such patients with another trained surgeon. Portal hypertension and coagulopathies should be approached with great caution.

Laparoscopic cholecystectomy can be performed with a very low morbidity rate, at least equal to that of the open procedure. The decreased operative discomfort may produce medical benefits, which remain to be identified. With adequate training, sound judgment, and highest priority given to patient safety, the risk of life-threatening or life-changing injury is minimal. Patient demand has fueled rapid dissemination of this technique throughout the country, but despite this, it is the responsibility of the surgical community to ensure that all surgeons receive the highest quality training and that the technique is applied appropriately.

Acknowledgments

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DISCUSSIONS

DR. WILLIAM MEYERS (Durham, North Carolina): Back in April at Vanderbilt University, the Southern Surgeons Club convened. This is a travel club of which one of the cofounders is Dr. DeBakey. At that time several participants reviewed their early preliminary experience with laparoscopic cholecystectomy. It was decided at that time to enter into, in a collaborative way, a prospective analysis of the perioperative complications.

There were 20 participants who ended up being in the study, representing 59 surgeons.

The surgeons just happened to be equally divided into academic *versus* private practice surgeons, with 10 coming from each, the definition of academic being the regular presence of residents participating in the surgery.

There were 1518 cases of laparoscopic cholecystectomy performed, with about one half performed by the private practice and one half by the academic surgeons. And the overall complication rate was 5.1%.

The number of conversions that were counted as complications was about 0.09%. That is there were conversions that were solely for the reasons of identification of anatomy and scarring that were not counted as complications.

There was one death in the series. That was a patient who underwent a laparoscopic cholecystectomy for what was thought to be subacute cholecystitis, and the patient did well initially for about 2 days and then died on the third postoperative day of a posteriorly ruptured 3 cm abdominal aneurism, which probably represented, in retrospect, a mistaken diagnosis.

The most common complication was superficial wound infection. The other complications were as listed, with 13 contributed from the conversion group, seven bile duct injuries, but there was actually an eighth injury that occurred after conversion to open cholecystectomy. There were a number of other complications, of which bowel injury is a prominent one. Four of them occurred in the series, two with the safety shield trochar and two without. We do not know the denominator of that, however. There were 31 other complications, of which many were very minor, including a delay in hospitalization of 1 day for a preoperatively arranged cardiology consultation.

As mentioned, the bile duct injury number was 7, representing 0.5% of the total group. Four of those injuries were recognized at the time of laparoscopic cholecystectomy and immediately converted and repaired with simple repairs, two of which required T-tube insertion. Three were unrecognized and represented significant complications.

The injuries occurred in cases 2, 3, 10, 12, 13, 25, and 43 in various surgeons' experiences. The exact bile duct injury rate was overall 0.47%. The unrecognized injury rate was 0.2%. The injury rate in the first 13, the unlucky 13 of anybody's series, was 2.2%. And after 13, 0.1%, which is favorable compared to the conventional rate of 0.2%.

The only difference between the academic and the private practice group was in mean operative time. Academicians were slower, averaging about 35 minutes or longer per case.

One glaring observation is the relatively low incidence of common duct disease found either before or during operation of only 1.8% compared to the expected 8% to 16%. And in the short time of follow-up, there has been a retained stone rate of 0.04% that has been recognized. I think we have to be alerted to that possible complication.

As has been shown previously in others' data, in the large group, the hospital stay is significantly shortened, with about 14% of patients discharged on the same day of hospitalization.

DR. RANDLE VOYLES (Jackson, Mississippi): This certainly is an important meeting, for this is the first presentation of laparoscopic cholecystectomy at the Southern Surgical Association, and I congratulate the authors in each of the three papers on their presentations.

It is particularly important that we sort out specific criteria for successful as well as a cost-effective application of this procedure across the country. For it is rapidly becoming available and it may be easier to teach someone how to do this procedure in a cost-effective fashion rather than reteach them later.

I will limit my discussion to three largely technical areas of this procedure. My data base for comments is a series of 500 patients completed in Jackson, Mississippi with no ductal injuries and no deaths.

It is increasingly clear that there is probably no patient benefit with laser dissection of the gallbladder. As many of you know, I have been doing an informal survey between sessions of this meeting. There are basically three categories of laparoscopic surgeons here.

There is the one group of surgeons who started with electrocautery and have continued with it. The second group, of which I am part, started off with laser and switched over to electrocautery and is not going back. And then there is a third group of surgeons, laser proponents who have limited experience with electrosurgical dissection.

I have also included in my informal survey the additional patient cost of laser dissection for the gallbladder. It starts at $250.00 in Nashville, where Dr. Graves is—and perhaps they have an additional benefit of cheaper costs because they got into the lasers earlier and perhaps purchased their equipment more cheaply. But it extends up to $1100 in some of the centers, where the expensive disposable fibers are used.

Again there is no claim of patient benefit by any of the surgeons using laser dissection over electrosurgical dissection.

The final question that I would raise concerns the business of operative cholangiography. Bill Meyers just noted that only 2% of patients seem to have common duct stones. So why are we going to be doing cholangiograms in the other 98%? Well one reason is to prevent injury, but Dr. Graves, I would quibble with the data supporting the case for routine operative cholangiography.

Dr. Graves I would quibble with you a bit about your own data. It appears to me that your cholangiogram might well have been the source of the injury rather than have prevented it.

Because the incidence of common duct stones seems to be so low, it seems to be important to develop more sensitive clinical parameters to determine who does not have common duct stones.

DR. DAVID ADAMS (Charleston, South Carolina): In 1987 Philippe Mouret performed laparoscopic cholecystectomy in Lyon, France. In 1988, as has already been mentioned, DuBois in Paris and Périssat in Bordeaux joined Mouret in carefully advancing the frontiers of this new technique.

The initial French experience has been analyzed recently by Professor Perisot and his additional data to support the conclusions that have been presented today. Périssat noted a 0% mortality rate, a 4.8% morbidity rate, and a 6.4% conversion rate in 2300 laparoscopic cholecystectomies, which were performed by 20 surgeons during a 3-year period.

One per cent of patients required open operations for complications of laparoscopic cholecystectomy, an issue that requires close scrutiny, as Dr. Graves and Dr. Jones have done today.

The Achilles heel of laparoscopic cholecystectomy, of course, is accidental injury of the common bile duct, and the questions I wish to ask Dr. Graves and Dr. Jones relate to this issue.

That is, does operative cholangiography prevent common bile duct injury during laparoscopic cholecystectomy and, thus, is cholangiography mandatory?

Will experience and better techniques improve the cholangiogram completion rate?

DR. JOHN WILSON (Atlanta, Georgia): My comments will involve three issues that have already been raised primarily by Dr. Graves, and they are predicated on our experience in laparoscopic cholecystectomy. Also I would like to present a few statistics that are the basis for my comments.

The pros of the procedure have been pretty well outlined. And I will not belabor this, but our statistics compare with most of those that have been presented. We have less than one day hospitalization. Actually 28% were done as true outpatients, and 87% of our patients returned home within 24 hours.

The cosmetic effect, the cost, the short term in the hospital, short time to return to work, all have been mentioned and are the advantages of this procedure.

The disadvantages concern the morbidity risks that are associated with the procedure. This has been our experience in our first 600 laparoscopic cholecystectomies that were done at Georgia Baptist Medical Center.

I think you can see from this that there were no common duct injuries. And, incidentally, these statistics have held true pretty much all the way with our continuing experience. There have been no common duct injuries, no deaths, and no postoperative bleeding.

The one small bowel injury was associated with adhesion, which was not done as part of the removal of the gallbladder but was done as an ancillary procedure, but at the time of cholecystectomy, and was recognized and repaired at that time.

The frank hematoma was a result of postoperative anticoagulation therapy and was due to suspected pulmonary embolus, which was not the case.

We used these statistics to make our second comment because we submitted our experience and it was returned as not appropriate for this program. However we think we need to share these statistics because it has to do with what I would like to say next, and that is that we think our good experience—and we feel that it is a very good experience—has been due primarily to the method with which we approached this. This has been a cooperative effort by all the surgeons in our hospital and was started as such. We agreed from the beginning that we would help each other; we would assist, we would observe, and we would criticize. And these are the individuals who have been the core of this experience.

I must note that Drs. Mason and Duncan were the progenitors of our program, and Dr. David Baird is one of our residents. Dr. Eddie Reddick in Nashville, who precipitated our interest in this procedure, was kind enough to allow Dr. Baird visit and work with him for a month and sent him home loaded with a lot of good information that has been essential to our success.

That it is the way we have gone about it that has made it successful to us. We have helped one another; we have offered the operative experience to other members of the surgical community.

We offered courses. I would like to say that a weekend course in laparoscopic cholecystectomy does not endow one with the ability to do a laparoscopic cholecystectomy. Rather the way to learn this is working with other surgeons who have experience in this particular procedure.

One final question, and that is a much broader issue that was raised by Dr. Graves. What have we learned from all of this and where do we go from here?

It is a short memory that can not recall gastric freezing, ligation, or the internal mammary artery for angina, and a few other very popular but short-lived procedures. This is here to stay and in the patois of the Southern Surgical Association, we could say that this is an elegant procedure, because it is.

It does have a dark side, however, because there have been some fallout of future shock effect on the average practicing surgeon who finds himself in the awkward position of needing to learn the procedure, which the public demands and which is of benefit to the patient. We are opening a whole new era here in intraoperative procedures.

Laparoscopic cholecystectomy goes far beyond being a new way to take out the gallbladder. We have gained the ability—those of us who experimented with the primitive peritoneal scope in the late 1940s and early 1950s can appreciate this to operate from outside the abdomen.

The video camera and intraperitoneal lighting has had a tremendous impact, for now we can operate on the inside of the peritoneal cavity from the outside. Not only that but we can have multiple individuals participating in that operative procedure, and we ensure that everyone in the operating room knows the procedure.

When your scrub nurse who has helped on 1000 gallbladders and handed you the proper instrument time after time but looks at you in amazement and says, "Gee, is that what's been going on in that hole all these years?" you know you have turned a page in surgical history. And the potential for what will occur is the thing that we must direct our attention toward.

It has the potential for a great deal of benefit for patients and a great deal of harm. And that new trunk that we are opening can be Pandora's Box or it can be a treasure chest, and it will take the leaders in surgery to define what is and what isn't. We must learn how to evaluate procedures quickly. We must disseminate that technical knowledge to our practicing surgeons in the field.

We are faced again with that same basic question. Not is this a procedure that can be done, but is it a procedure that should be done and where?

DR. CARLOS CHAVEZ (Brownsville, Texas): I rise to inject a word of caution, in contrast to what has been said. In comparing orthodox cholecystectomy or open cholecystectomy with laparoscopic cholecystectomy, it seems that the main issue revolves around two main factors. The first is the length of postoperative hospital stay, and the second is the recovery after surgery.

If we change our traditional attitude of dismissing our patients after 3 or 4 days, or even after 6.1 days, as somebody mentioned, after surgery and offer them an early dismissal, then no significant difference would be apparent in these two approaches.

The size of the incision may play a role in the postoperative recovery of the patients. When a mini-incision is made for the traditional cholecystectomy, then we should expect a quick recovery similar to those patients undergoing laparoscopic cholecystectomy.

General anesthesia is still necessary for both types of procedures, which are still done in the operating room. In the last 5 months, Dr. Erwin and I performed 27 cholecystectomies, 22 of which had mini-incisions of 5 cm, that is, 2 inches long. One half of these patients had an incision that was 4 cm long. That is just a bit larger than the size of incision for a laparoscopic cholecystectomy. Four of these patients were men and 18 were women.

The longest incision in the whole group was 14 cm, and this was done in a patient who weighed 256 pounds. In this patient, that size incision looked like a mini-incision.

In 20 patients operative cholangiograms were done.

As you can see, the criteria for laparoscopic cholecystectomy are very rigid at this point.

However, for a mini-cholecystectomy, all that is required is the standard equipment in the operating room a sterile rule to measure the length of your incision, the head lamp, which is optional but helps to provide the good visual field, some clip appliers, and a little bit of patience.

It is amazing the panic and euphoria among surgeons to jump into the bandwagon terrorized by referring physicians of patients who like to have laparoscopic procedures.

It is commendable to look for new modalities in treatment, but it is also commendable, perhaps more so, to improve techniques or procedures we know have worked well.

DR. JEANNE F. BALLINGER (Closing discussion): I would like to respond to Dr. Voyles' question about educating the public about laser use. In our group we began with the laser but now strictly use electrocautery, and we think it is important to educate the public that this is laparoscopic cholecystectomy and not laser cholecystectomy.

We always use in our group, as far as the disposable trochars, the radiolucent 5-mm trochar in the right upper outer quadrant for visualization through the cholangiogram. One of our members uses three nondisposable trochars. When we reviewed our cost in preparing this document, the other two members are considering using the nondisposable trochars as well, although there does seem to be more air leak sometimes, as mentioned, with the nondisposable trochars.

I would like to differ with Dr. Voyles on the cholangiogram being the cause for the injury to the common duct in our series. In fact the surgeon thinks that if the cholangiogram had not been obtained, he might have cut the common duct in half. We have not been as happy with our success rate with cholangiograms and think the new technique of aspirating the bile and putting a needle into the neck of the gallbladder and under direct fluoroscopy watching the dye flow into the ducts may, in fact, enhance our definition of the anatomy.

We think laparoscopic cholecystectomy is an exciting new addition to general surgery but have great respect and caution for the technique.

As Dr. DeBakey stated in his presidential address, the most important person in all our endeavors is the patient. It is imperative that the safety of the patient be the primary concern in every case.

Laparoscopic Cholecystectomy

Treatment of Choice for Symptomatic Cholelithiasis

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Our initial experience with laparoscopic cholecystectomy (LC) for symptomatic cholelithiasis has involved 152 patients. Patient age ranged from 17 to 83 years; most were female (78%). Their average weight was 170 pounds (range, 75 to 365 lbs.). Twenty-two per cent had a single gallstone, while 9% had two to three stones and 64% had more than three stones. Exclusion criteria initially included upper abdominal scarring, severe acute cholecystitis, choledocholithiasis, and inability to tolerate general anesthesia. The first two of these are now only relative contraindications with increased experience. Thirteen of the one hundred fifty-two procedures (8.5%) required conversion to an open operation. Average time of operation was 138 minutes. Intraoperative cholangiography was attempted in 78% of cases and was completed successfully in 66% of those attempted. There have been no deaths. The complication rate has been low: 4% major, 0% life-threatening, and 7.2% minor complications. Postoperative analgesic requirements are remarkably low: 36% of patients required no narcotics after leaving the recovery room. Eighty-seven per cent of patients successfully undergoing LC were discharged by the first postoperative day. Most patients resumed normal activities within 1 week after discharge. Laparoscopic cholecystectomy offers the majority of patients with symptomatic cholelithiasis an improved treatment option, resulting in significantly less postoperative pain, hospitalization, and recuperation time.

From the Department of Surgery, University of Virginia Health Sciences Center, Charlottesville, Virginia

LAPAROSCOPIC CHOLECYSTECTOMY (LC) was first introduced in France in 1987 by DuBois et al.[1] Since then the procedure has created a tremendous amount of controversy and attention in the surgical community, especially in the United States since late 1989. Many biliary surgeons have either already introduced LC into their practice or sought opportunities to learn the procedure. There has been a rapid proliferation of training courses offered to teach the procedure, as well an excess demand on instrument companies for equipment. It is estimated that within the last 18 months the number of laparoscopic cholecystectomies done in the United States has increased from less than 500 to more than 20,000. In the Commonwealth of Virginia, for example, the first LC was done in February of 1990, and by November 1990 we conservatively estimate that more than 600 LC procedures were performed (personal communication).

There have been few reports since that of Dubois documenting the safety and efficacy of LC in the surgical literature. Reddick and Olsen reported the first large series in this country.[2] Berci and Sackier[3] and Perissat[4] also recently reported their respective experiences, as has Zucker.[5] Recently a collected series of more than 1500 cases of successful LC procedures from 20 different medical centers in the Southeastern United States has been submitted for publication in the literature.[6] Because more thorough reporting of results of LC at individual medical centers is needed, we report the experience at the University of Virginia Health Sciences Center.

Methods

The experience in performing laparoscopic cholecystectomy at the University of Virginia began when two of the coauthors (BD Schirmer and SB Edge) underwent training in the procedure at a course taught by Drs. Airan, Ko, Berci, and Sackier in Chicago in January 1990. After appropriate training of a complete surgical team once back in Virginia, the first operation was performed on February 23, 1990. It is important to emphasize the critical nature of the team approach to this procedure. All members of the team, including nursing personnel and operating room equipment technicians, should be fully versed in the operation and vagaries of the equipment used in the performance of LC.

Using the techniques described below, 152 patients have undergone attempted LC. Indications for LC have included symptomatic cholelithiasis (145 cases), biliary dyskinesia with documented abnormalities of the gallbladder on cholecystokinin stimulation test or *via* endoscopic retrograde cholangiopancreatogram (ERCP) findings of crystals in the bile (3 cases), and acute acalculous cholecystitis (4 cases). Contraindications for LC are listed in Table 1. Initially patients with acute cholecystitis, upper or mid-abdominal scarring, or known choledocholithiasis were not considered for LC. However, with increasing experience, we now consider patients with the former two conditions to be candidates for LC. Those with choled-

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TABLE 1. *Laparoscopic Cholecystectomy*

Contraindications
Absolute
Inability to tolerate general anesthesia
Required concomitant upper abdominal operation
Relative
Coagulopathy
Upper abdominal scar
Acute cholecystitis
Choledocholithiasis

ocholithiasis are potential candidates, if successful ERCP and sphincterotomy with preoperative common duct clearance can be achieved. Patients with asymptomatic gallstones are not deemed to be candidates for LC.

The major items of equipment that are required for laparoscopy in general and LC in particular are listed in Table 2. Positioning of the equipment and the surgical team members are shown in Figure 1. There is flexibility as to which side of the patient the camera, light source, and insufflator are placed. Dual TV monitors are optimal but we routinely perform the procedure with a single monitor to the patient's right.

The procedure begins with the induction of general anesthesia, which has been used in all cases of LC. A Foley catheter and orogastric tube are placed to minimize the risk of injury from laparoscopy. The Veress needle is used to create a pneumoperitoneum, using standard techniques of laparoscopic insertion. Insertion into the umbilicus or umbilical ring directly is optimal for Veress needle placement. Presence of a midline scar in the area of the umbilicus necessitates use of an alternate secondary site for Veress needle placement.[7] The right lower quadrant location is optimal in such situations; insertion of a 5-mm telescope allows confirmation of a safe location near the umbilical or midline area for 10-mm trocar and telescope insertion. The 10-mm telescope is needed to provide adequate light and visualization to proceed safely with LC. Generally we have used a 0 degree lens, but at times a 30 degree lens may offer advantages to better visualize the porta hepatis area. Another alternative in the case of periumbilical scarring is the use of a small incision into the fascia under direct vision and use of a Hasson cannula for the trocar.

TABLE 2. *Laparoscopic Cholecystectomy*

Equipment Needed
Therapeutic laparoscopy set
High-flow insufflator
Video camera
Two monitors
Good light source
Special biliary instruments

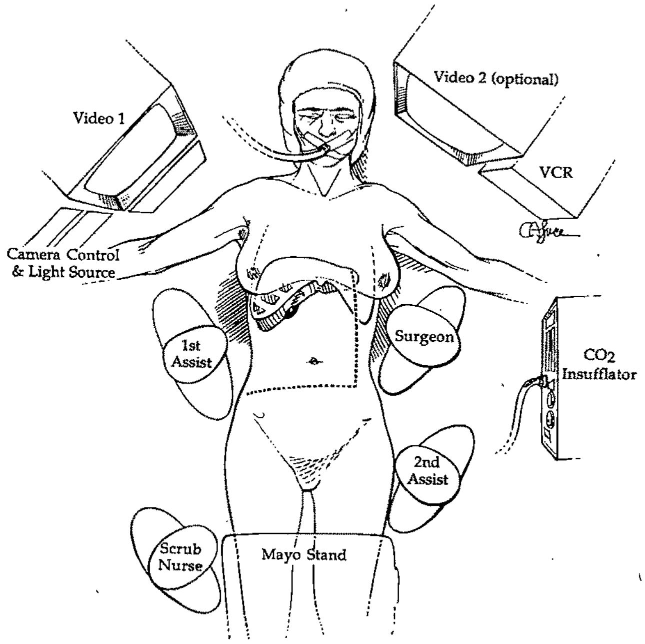

FIG. 1. Position of the operating team and major items of equipment during laparoscopic cholecystectomy.

The pneumoperitoneum is established carefully using CO_2 gas and diagnostic laparoscopy is performed. The secondary trocars are placed under direct laparoscopic vision. Recommended locations for these trocars are illustrated in Figure 2. Trocar locations may have to be varied based on patients body habitus or particular anatomy.

Exposure of the gallbladder is achieved through use of two 5-mm grasping forceps. The first, which ideally should be ratcheted for subsequent ease of fixation, is inserted through the lower lateral trocar and used to retract the fundus of the gallbladder upward toward the diaphragm. This allows exposure of the infundibulum area of the gallbladder. Use of the reverse Trendelenberg position, and, sometimes, rotation of the operating table to the patient's left (toward the surgeon) can be helpful. A second 5-mm grasping forceps is used to elevate the infundibulum of the gallbladder in a dynamic fashion, allowing optimal exposure of the triangle of Callot through rotation and upward traction (Fig. 3).

Dissection of the peritoneum overlying the cystic duct and artery then begins, assuming any omental adhesions to the anterior surface of the gallbladder have been taken down using the grasping forceps, scissors, and cautery as necessary. Some of the instruments used in the operation are illustrated in Figure 4. In dissecting the cystic duct and artery free from their surrounding peritoneum and fat, either the scissors, spatula, or hook instruments are helpful. All are available with insulated shafts and connectors to allow use of monopolar cautery during dissec-

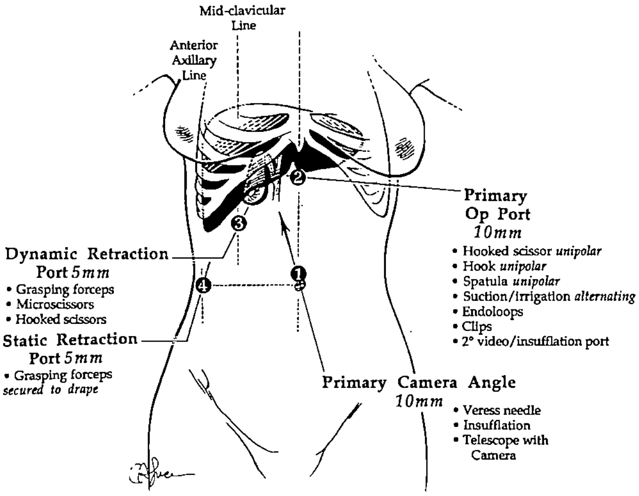

FIG. 2. Location of trocar sites during routine laparoscopic cholecystectomy and the instruments used at each site.

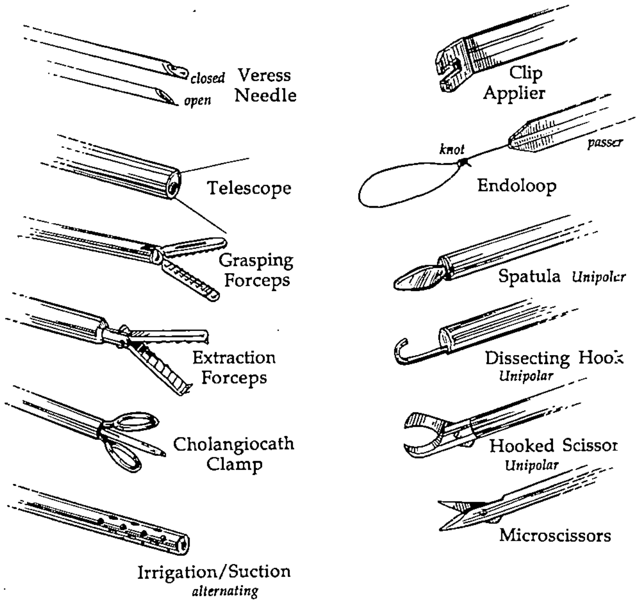

FIG. 4. Working ends of many of the instruments used in laparoscopic cholecystectomy.

tion. In addition the hook and spatula instruments, available from Karl Storz Inc. (Culver City, CA), are designed with irrigation or suction ports built into the instrument.

Once cystic artery and duct are identified, we address the most superficial structure first. Figure 5 illustrates dissection of the porta hepatis, clipping of the cystic artery, isolation of the cystic duct, and placement of a titanium clip on the cystic duct. Use of the Auto Suture automatic multifire endoclip applier (U.S. Surgical Corp., Norwalk, CT) avoids the need for reintroduction through the trocar for multiple-clip application.

Intraoperative cholangiography is recommended, particularly early in the surgeons's experience with LC, when orientation and identification of the anatomy may be more uncertain. The microscissors are used to cut a hole in the cystic duct just below the clip, The Olsen cholangiography fixation clamp (Karl Storz) facilitates cannulation of the cystic duct with a catheter (Fig. 6). In our experience a 6F straight ureteral dilator with a single end hole is most useful. Cannulation of the cystic duct is most easily performed from the fourth (midclavicular) trocar. There may be difficulty in performing cannulation of the cystic duct due to size limitations and interference from the spiral valves of Heister. A flexible guidewire may be helpful in such cases.

Once cholangiography is accomplished or the decision to forgo it is made and the anatomy clearly defined, the

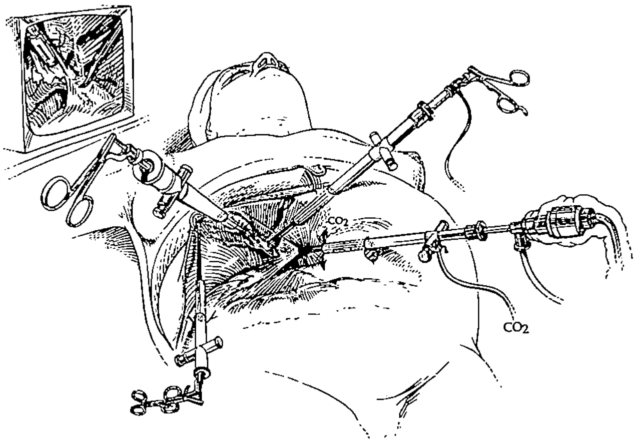

FIG. 3. Standard four-trocar technique of laparoscopic cholecystectomy and exposure of the triangle of Callot.

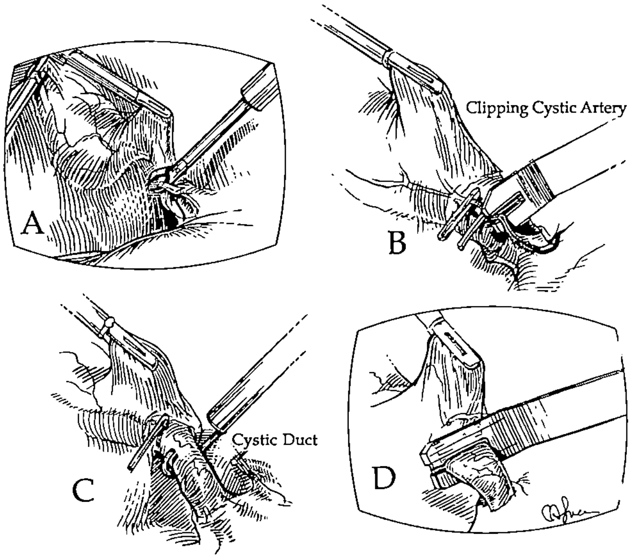

FIG. 5A–D. (A) Dissection in the area of the cystic duct and artery to define these structures. (B) Placement of clips on the cystic artery. (C) Further isolation and dissection of the cystic duct with the hook instrument after having divided the cystic artery. (D) Placement of a single clip on the proximal cystic artery.

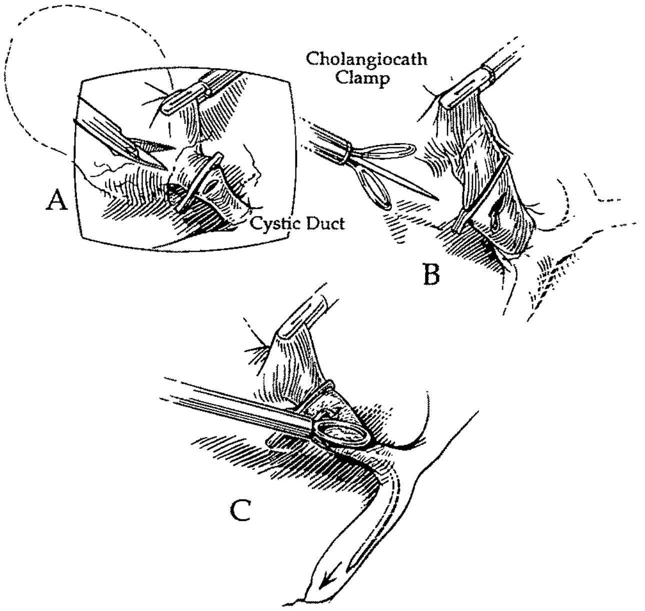

FIG. 6A–C. (A) Microscissors used to cut an opening in the cystic duct. (B) Insertion of the cholangiocatheter passed through the cholangiogram clamp for the performance of intraoperative cholangiography. (C) Cholangiogram catheter in position in the biliary tree, held securely in place with the clamp.

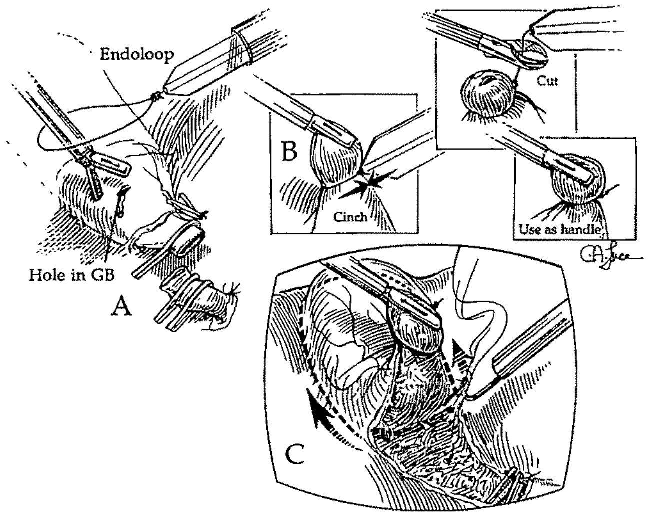

FIG. 7A–C. (A) Use of an endoloop to control bile spillage from a hole in the wall of the gallbladder. Endoloop is inserted and grasping forceps passed through the loop. (B) Plastic passer is used to cinch the knot down around the forceps, which have grasped the gallbladder wall at the site of the hole. The tie is then cut and the area of tissue may be used as an area for retraction with relative safety. (C) Elevation of the infundibulum area of the gallbladder assists in exposure for dissection of the gallbladder off the liver bed, done here using the hook instrument for dissection.

cystic duct is divided between clips, two on the proximal (patient) side and one on the distal (specimen) side. The gallbladder is again grasped by the infundibulum and elevated to allow optimum exposure for dissection off the liver bed. Should a rent be made in the gallbladder from too vigorous a retraction or the presence of friable tissue, a tie (endoloop) is useful for securing the hole closed and providing an area of tissue relatively safe for further retraction (Fig. 7). Dissection of the gallbladder off the liver bed is in particular facilitated by coordinated efforts of the surgeon and assistant in terms of exposure, traction, and countertraction. Our experience has involved only the use of monopolar cautery for this portion of the operation, although others have advocated use of a laser for this dissection.[2] When the gallbladder dissection is nearly completed, the liver bed and porta hepatis once more are inspected carefully for any signs of hemorrhage and to ensure that the clips remain securely in place. Cauterization, irrigation, and suctioning are performed as necessary to achieve a hemostatic liver bed. The final strands of peritoneum attaching the gallbladder to the liver bed then are divided.

Removal of the gallbladder usually is done through the umbilical trocar site. This provides the flexibility of most easily extending the usual 10-mm incision in the periumbilical area, as is frequently necessary for gallbladders containing multiple or large stones. The telescope is repositioned through the epigastric trocar site and a large or traumatic grasping forceps is used to retract the infundibulum area of the gallbladder into the 10-mm trocar (Fig. 8). The entire trocar is pulled out through the abdominal wall, suspending the gallbladder through the abdominal wall. Allis clamps grasp the portion of the gallbladder above the skin and prevent retraction while the grasping forceps and trocar are removed. A small opening cut in the cystic duct area allows aspiration of all bile from the gallbladder. Enlargement of the incision is per-

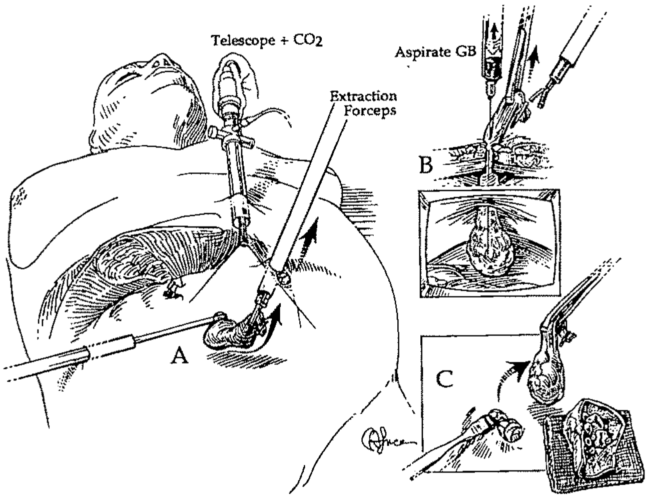

FIG. 8A–C. (A) Extraction of the gallbladder begins by using a large grasping forceps passed through the umbilical trocar to grasp the infundibulum of the gallbladder. The gallbladder is pulled partially into the trocar and the trocar retracted. (B) Bile is aspirated from the gallbladder after it is partially removed and the infundibulum is exposed above the skin level. (C) Extraction of the decompressed gallbladder.

formed only as needed to allow the removal of the intact gallbladder using gentle to moderate traction.

After gallbladder removal, a finger is placed through the umbilical trocar site to preserve the pneumoperitoneum adequately enough to visualize removal of the remaining two 5-mm trocars. Peritoneal sites are inspected for hemostasis after trocar removal. Finally the telescope is removed and the pneumoperitoneum decompressed.

Infiltration of the trocar sites with 0.5% bipuvicaine aids in postoperative analgesia. If possible we close the fascia of the 10-mm sites with an absorbable 0 or 2-0 suture. Skin sites are closed with running or interrupted subcuticular absorbable suture and sterile dressings are applied.

It has been our practice to use intravenous antibiotic prophylaxis for LC procedures. Also sequential compression devices for the lower extremities as well as subcutaneous heparin are recommended as prophylaxis against deep-vein thrombosis.

There are several particular safety precautions that should be stressed during LC procedures. As with all laparoscopic procedures, the anesthesiologist should have the capacity to monitor end-tidal CO_2 content because a sharp increase in this value during the case signals either subcutaneous emphysema with massive CO_2 absorption or CO_2 embolism into the vascular system. The pH level may decrease but appropriate treatment is hyperventilation. Intravenous sodium bicarbonate should be avoided in these circumstances.

Cardiac monitoring is imperative during laparoscopy because the creation of a pneumoperitoneum has a known low but real incidence of inducing arrhythmias. Immediate treatment includes decompression of the pneumoperitoneum.

Monopolar cautery has the inherent danger of skin burns, and thus grounding pads should be checked for secure placement. The fiberoptic light source produces a significant amount of heat, and the cable tip can ignite the drapes in a matter of seconds if allowed to come in unprotected contact with them while the light source is on. Similarly the tip of the telescope is a source of heat and care must be taken that it is not inadvertently in contact with an intra-abdominal organ for any significant length of time.

Using these operative techniques, LC was performed in 152 cases. At least one coauthor faculty member was involved in all cases. Resident participation occurred in all but the first few LC procedures. Patient data was recorded at the time of discharge and follow-up visits and stored in a computer data base program. Parameters included sex, age, weight, surgeon, number of gallstones, presence of abnormalities in preoperative liver function tests, American Society of Anesthesiology (ASA) class,[8] length of operation, performance of intraoperative cholangiography, use of drains, presence of adhesions or acute inflammation, success in completing LC, length of postoperative hospitalization, postoperative use of pain medications, and adverse events or complications. Operative death is defined as a death occurring within 30 days of operation or later if directly resulting from the sequelae of surgery. Major complications are defined as those events resulting in a prolongation of hospital stay or readmission to the hospital. Patient data below, where appropriate, are expressed as mean ± SEM. Statistical analysis was performed using either one-way analysis of variance for comparison, Chi square for assessing significance of observed versus expected values, or linear regression for correlation as appropriate. Significance was defined as $p < 0.05$.

Results

Of the 152 patients undergoing LC, 118 were female (78%) and 34 were male (22%). Ages ranged from 17 to 83 years, with an average age of 43.2 ± 1.2 years. Average weight was 170.3 ± 3.8 pounds with a range of 75 to 365 pounds. Of the 152 patients, 143 had the diagnosis of cholelithiasis made before operation by ultrasound, while one patient each was diagnosed as having cholelithiasis by plain film and oral cholecystogram (OCG), respectively. Two patients had biliary dyskinesia with diagnostic abnormalities of gallbladder emptying by OCG. One patient had pancreatitis and ERCP showing stones, which were evacuated before operation. Four patients had either acute or chronic acalculous cholecystitis with preoperative ultrasound or radionuclide scan to confirm the clinical picture.

Thirty-four patients (22.4%) had a single gallstone present by preoperative testing. Fourteen (9.2%) had either two or three stones, while most patients (63.8%) had more than three stones within the gallbladder. Pathologic examination revealed no carcinoma of the gallbladder. One case of adenomyoma of the gallbladder was diagnosed pathologically.

Four patients (2.6%) had a documented episode of jaundice before operation. Eight (5.3%) had a documented episode of pancreatitis before performance of LC. Thirty patients (19.7%) had abnormalities of one or more preoperative liver function tests. Laparoscopic cholecystectomy was not attempted in the setting of ascending cholangitis or clinical jaundice and concurrent signs of inflammation of the gallbladder.

Patients were classified before operation by ASA classification[8] (Table 3). Most patients were in the ASA class I (46, or 30.3%) or II (88, or 57.9%) categories, but 18 (11.8%) were ASA class III.

Operative Time

Operative time (from time of incision for Veress needle placement to time of dressing) was an average of 138 ± 4

TABLE 3. *Influences of Increasing Experience on Operative Time*

		First Half of Cases		Second Half of Cases		All Cases	
Suregon	Success	OR Time (min)	n	OR Time (min)	n	OR Time (min)	n
1	Successful						
	LC only	123 ± 5	39	121 ± 6	40	122 ± 4	79
	All	130 ± 6	43	124 ± 7	43	129 ± 4	86
2	Successful						
	LC only	151 ± 11	18	126 ± 11	19	138 ± 8	37
	All	150 ± 10	20	127 ± 10	20	138 ± 7	40
3	Successful						
	LC only	162 ± 13	8	150 ± 13	7	156 ± 9	15
	All	173 ± 15	9	172 ± 23	8	172 ± 14	17
4	Successful						
	LC only	153 ± 13	4	140 ± 9	4	145 ± 9	8
	All	160 ± 12	5	140 ± 9	4	150 ± 10	9

LC, laparoscopic cholecystectomy; OR, operating room.

minutes. The range was 52 to 320 minutes (Fig. 9). Thirty operations took 100 minutes or less. The longest case actually took longer but a time estimate was established for the attempted LC, conversion to open cholecystectomy, and common duct exploration. Subsequent duodenotomy and sphincteroplasty were required for a stone impacted in the ampulla of Vater. Thirteen cases required more than 200 minutes. In six of these, LC was converted to open cholecystectomy. Of the other seven, one represented a surgeon's first case, and one had significant delays due to multiple cholangiograms required due to failure of dye to empty into the duodenum. Acute cholecystitis (two cases) and severe adhesions and scarring (two cases) were other causes that delayed operations beyond 200 minutes.

The data were analyzed to determine whether intraoperative cholangiography had a significant impact on the length of operative time. These data are summarized in Figure 10. When all procedures were considered, there was a significant difference ($p < 0.002$) between operative time for cases in which a cholangiogram was completed ($n = 79$) compared to those cases in which it was just attempted ($n = 40$) or not attempted ($n = 33$). When successfully completed LC procedures alone were analyzed, there was still a significant difference ($p < 0.004$) between the group in which cholangiography was completed ($n = 70$) compared to groups in which it was only attempted ($n = 39$) or not attempted ($n = 30$).

Other factors were analyzed as to their effect on operative time. To determine the influence of increasing operative experience on LC operative time, cases were grouped according to the primary surgeon involved. Table 3 shows the data when the first half of each surgeon's experience was compared to the last half. None of the surgeons showed a significant decrease in operative time with increasing experience, including surgeon 2 ($p = 0.13$).

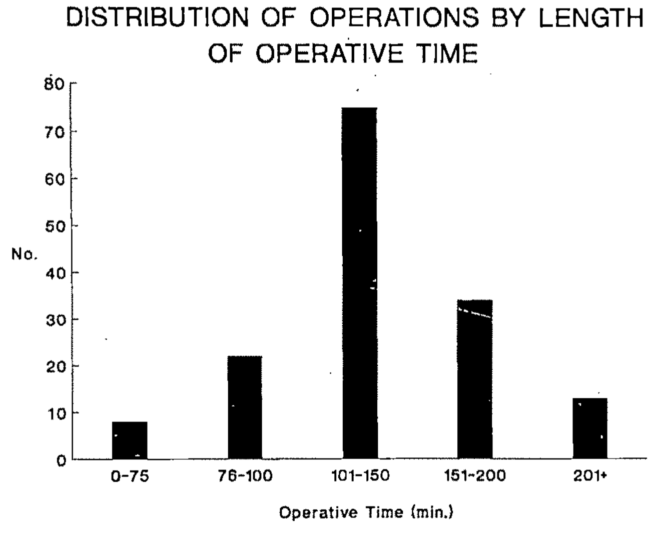

FIG. 9. Distribution of all operations by length of operative time. Most operations took between 101 and 150 minutes.

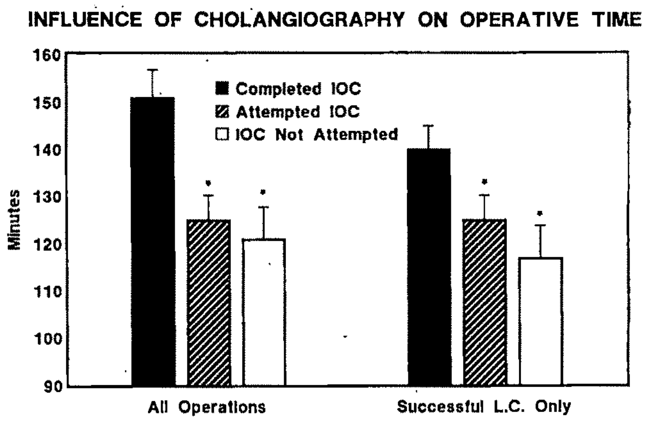

FIG. 10. Graph showing the length of time required for operations in which an intraoperative cholangiogram (IOC) was not attempted, attempted but not completed, and completed. * Denotes p value less than 0.05 in comparing the completed to the other two groups for both all operations and for successful LC cases only.

These comparisons held true when analysis was confined to successfully completed LC cases as well.

There was a significant difference between the average operative time for the surgeon with the most experience when compared to the other surgeons with less experience, when successful LC cases alone were analyzed ($p = 0.0007$) and all cases were compared ($p = 0.003$). There also was a significant difference between the two surgeons with the most operative experience when compared to the two with the least operative experience when either all cases ($p = 0.007$) or successful LC cases only ($p = 0.016$) were compared. One of the least experienced surgeons did have significantly differently longer operating times compared to the group as a whole for all cases ($p = 0.008$) and successful LC cases ($p = 0.035$).

Figure 11 shows regression analysis between operative time and number of LC cases using each surgeon's experience as a data point. There was not a significant correlation between individual surgeon's experience and length of operative time by regression analysis ($p = .104$).

Acute cholecystitis and edema of the gallbladder were present in 12 of the cases in which LC was attempted. The mean operative time for this subset of procedures was 180 ± 13 minutes, significantly longer than the average for those patients without acute cholecystitis (134 ± 4 minutes, $p < 0.0006$). Patients with preoperative elevation of liver function tests ($n = 30$) similarly had a significantly increased average duration of operation (162 ± 8 minutes) compared to those with normal preoperative liver function tests (132 ± 4 minutes, $p < 0.0012$).

Patients in whom no significant adhesions or scarring were noted around the gallbladder at the time of surgery had a significantly decreased mean operative time (116 ± 6 minutes, $n = 55$) when compared to the patients with these findings at the time of surgery (150 ± 4 minutes, $p < 0.0001$).

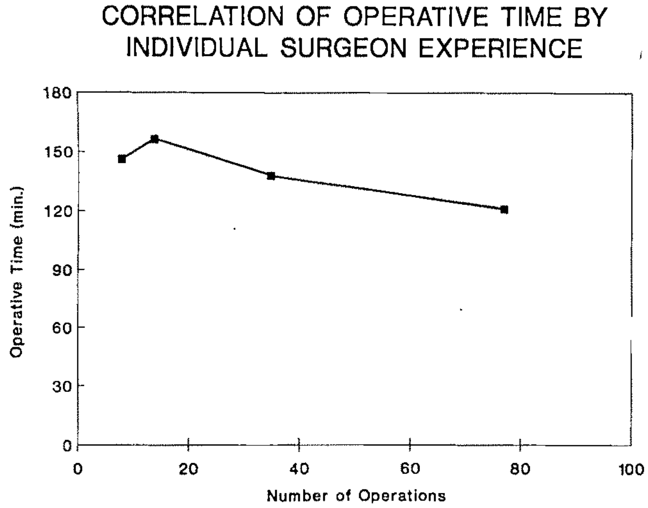

FIG. 11. Graph of the correlation of operative time by each surgeon's experience. There was no significant correlation between data points by regression analysis ($p = 0.10$).

Morbidity and Mortality Rates

There were no operative deaths in our series of LC procedures. Major complications numbered six, for an overall rate of 3.95%. One patient, the 31st in our series, suffered a laceration of the side of the common bile duct during dissection of a cystic duct lying immediately in front of the unidentified common duct. The injury was easily seen when the cystic duct was divided and the procedure was converted to an open operation with placement of a T tube into the injury site. The patient made an uneventful recovery and has done well for more than 6 months. There have been no other major complications directly as a result of intraoperative events.

One patient was readmitted 2 days after discharge with a clinical diagnosis of probable bile peritonitis. During the patient's operation, there was no major spill of bile. Two other patients were readmitted to the hospital with abdominal pain after discharge. One had a diagnostic esophagogastroduodenoscopy that showed an active duodenal ulcer. A second had simultaneous elevation of liver function tests on admission, but bilirubin levels were normal and follow-up ultrasound examinations showed no evidence of biliary obstruction. In this case it is presumed symptoms resulted from passage of a small common duct stone in the immediate postoperative period.

One patient was readmitted 24 hours after discharge with a fever. This subsided within 12 hours and he was hospitalized for only 1 day. The other major complication involved a woman with multiple medical problems, including renal failure, who was on hemodialysis. At the time of her successful LC procedure she had acute cholecystitis. Postoperative hospitalization was prolonged and she continued to complain of severe abdominal pain. Finally 2 weeks after her LC procedure she underwent exploratory laparotomy for the persistent pain. There was no significant intra-abdominal disease found at the time of exploration.

Minor complications or adverse events numbered 11, for an incidence of 7.2%. Five patients had a single wound site that developed infection after operation. This was usually the umbilical trocar site. All were treated with local care with or without oral antibiotics.

Two patients developed intraoperative subcutaneous emphysema. These were the only complications noted to result directly from laparoscopy. In both instances the finding was diagnosed by elevations in end tidal CO_2 levels with accompanying palpable crepitus in subcutaneous tissues. In both instances successful completion of LC was possible and both patients recovered fully after a period of several hours of observation in the recovery room.

One patient developed a postoperative transient ischemic attack consisting of left facial nerve involvement. This resolved completely by the next day. One patient developed postoperative mild pulmonary edema that responded to appropriate diuretic therapy. Two patients developed intraoperative or immediate postoperative electrocardiographic (EKG) changes. Both were evaluated for perioperative myocardial infarction and both were ruled out by enzyme and follow-up EKG criteria.

Success of Laparoscopic Cholecystectomy

Laparoscopic cholecystectomy was completed successfully in 139 of 152 attempts in this series (91.5%). One obvious factor that contributed to a high rate of conversion to open cholecystectomy was acute cholecystitis. Five of the 13 conversions in the series were in patients with acute cholecystitis. Conversion to open cholecystectomy occurred in 5 of 12 patients with acute cholecystitis, or 41.7% of such cases. This conversion rate is significantly greater than would be expected based on the opening rate of the series overall ($\chi^2 = 18.18$, df = 1, $p < 0.001$).

Problems with the bile ducts resulted in conversion of two procedures to open laparotomies. The common bile duct injury was discussed above. In another patient the cystic duct was so short that clip occlusion was incomplete and a small bile leak could be seen. The cystic duct stump was sutured closed after conversion to an open procedure.

Intraoperative hemorrhage accounted for three conversions to open procedures. In one patient the hemorrhage was from the cystic artery stump, which could not be well controlled using laparoscopic means. In two others the liver bed was so scarred that significant intraoperative hemorrhage occurred.

One conversion to open cholecystectomy was done after the gallbladder tore and a significant number of stones and much bile spilled into the subhepatic space. Two other conversions to an open technique resulted from the discovery of choledocholithiasis during intraoperative cholangiography.

Preoperative factors that contributed independently to a significantly increased risk of conversion to open cholecystectomy included the presence of acute cholecystitis. Elevated preoperative liver function tests did not increase the risk of conversion to open cholecystectomy, nor did a body weight of more than 200 pounds. There was no significant difference between the rate of open cholecystectomy between surgeons. Patients classified before operation as ASA III did not have a significantly increased incidence of conversion to open cholecystectomy.

Postoperative Recovery

Most patients were discharged from the hospital on the first postoperative day if they had undergone successful completion of LC (Fig. 12). This group of 139 patients had an average postoperative stay of 1.28 ± 0.11 days. This included two patients discharged the day of operation. There were 13 patients discharged 2 days after surgery, many of whom were judged before operation to be ASA classes II(6) or III(3). One patient (ASA class II) stayed 3 days. Two patients (ASA classes II and III) stayed 4 days. One of the latter required ERCP after operation to evaluate persistent nonfilling of the duodenum by intraoperative cholangiography. The ERCP was normal. The second patient had postoperative dyspnea, mild pulmonary edema, and abdominal pain that took several days to resolve. One patient with severe von Willebrand's disease was hospitalized for 8 days after the LC procedure for cryoprecipitate therapy (no intraoperative bleeding). One patient, classified as ASA III, had persistent postoperative abdominal pain that eventually led to a laparotomy, as discussed above. Three of the five patients requiring more than 2 days hospitalization after successful LC were preoperative ASA class III, which was a significant independent risk factor.

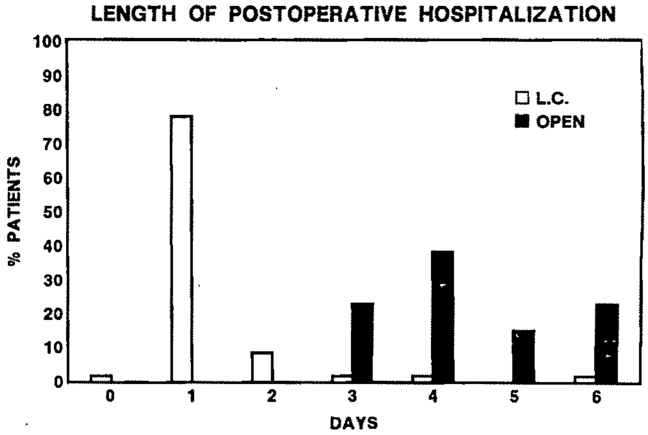

FIG. 12. Patient distribution according to the number of postoperative days before discharge. The significant difference in the distribution between patients undergoing successful LC and those undergoing conversion to open cholecystectomy can be seen clearly.

Patients who underwent conversion to an open cholecystectomy had a significantly longer postoperative hospital stay (5.15 ± 0.42 days) than patients who had successful completion of LC (1.28 ± 0.13 days, $p < 0.0001$). In this group there were 3 patients discharged 3 days after operation, 5 on postoperative day 4 and 2 on postoperative day 5. One patient with cerebral palsy had persistent postoperative vomiting after open cholecystectomy. After ruling out mechanical obstruction, he was discharged on the 14th postoperative day. One patient requiring open common bile duct exploration with duodenostomy and sphincteroplasty was discharged on the eighth postoperative day. One patient with multiple medical problems (ASA class III) had acute cholecystitis and required 6 days to recover from her operation.

Postoperative use of pain medication was recorded in this series. As shown in Table 4, 36% of patients undergoing successful LC did not require any narcotic analgesics, either oral or parenteral, after being discharged from the recovery room. Recovery room time was usually less than 2 hours following the operation. An additional 25% of patients took only oral narcotic medication. The group of patients who required intravenous narcotic medication for analgesia rarely used more than 6 to 8 mg of morphine or the equivalent. All patients who underwent conversion to open cholecystectomy required intravenous narcotic medication. Eleven of the thirteen used patient-controlled analgesia pumps for 2 or more days after operation.

Discussion

Shortly after Langenbuch performed the first successful cholecystectomy in 1882,[9] this procedure became the treatment of choice for symptomatic cholelithiasis. The last 100 years have seen few advances in the actual approach and conduct of cholecystectomy but have been marked by increasingly safe and efficient conduct of the procedure. Data from New York Hospital/Cornell Medical Center showed that the mortality rate for elective cholecystectomy in a large series of patients from 1978 to 1984 was 0.2%, which is decreased from an already low figure of 0.6% for the preceding 50 years.[9] It is against this standard of safety that all other innovations in the surgical treatment of cholelithiasis must be compared. Because our series numbers only 152 patients, final conclusions based on expected *versus* observed deaths for LC are not possible. However, because there have been no operative deaths in our series, and because our series has included operations on patients with significant medical problems (18 patients were ASA class III) as well as elderly patients (9 patients were 70 years or older), we conclude that to date there is no reason to suspect laparoscopic cholecystectomy will not prove as safe as standard open cholecystectomy.

Morbidity for elective open cholecystectomy is thought to be about 3% to 5%.[10] Our data show a comparable 4% rate of significant complications for LC. The consequences of most of the major complications in this series were not severe. Four of the complications involved readmission to the hospital and all of these patients did well with generally conservative therapy and observation. Intravenous antibiotics were given to only one patient in this group. One patient required an upper endoscopy to confirm an active duodenal ulcer, but no other patients in this group required invasive procedures. One other patient did undergo reoperation, and it was confirmed from the negative findings at open laparotomy that her persistent abdominal pain and probably also her lack of expected recovery following LC were due to her other significant active major medical problems.

TABLE 4. *Postoperative Pain Medications After Recovery Room*

Parenteral Narcotics	Oral Narcotics Only	No Narcotics
39%	25%	36%

There was one common bile duct injury in this series. This occurred during scissors dissection of the cystic duct. The injury was recognized immediately after division of the cystic duct, because only then could the common duct with its lateral laceration be seen clearly with the telescope. This case emphasizes that LC is a procedure with which visual feedback of surgical movements is essential and dissection without clear visualization behind a structure can result in such a complication.

The incidence of bile duct injury in the series was 0.66%, which is probably higher than the expected rate of such a problem for open cholecystectomy. The latter is generally thought to be between 0.2% and 0.25%, but may be higher.[11-13] Criticism of laparoscopic cholecystectomy from the surgical community has included the concern that bile duct injuries may become significantly increased with the procedure. It is possible that early in each surgeon's use of LC there will be an increased risk of bile duct injuries. Whether this risk translates into a significant problem with bile duct strictures and patients with long-term sequelae of bile duct injuries remains to be seen. However, based on our data, it would seem unlikely that this situation will occur because the only injury was easily recognized, appropriately treated, and resulted in no long-term sequelae as of this time.

The safe propagation of performance of LC in the months ahead is important if the procedure is not to fall into disfavor from an increased incidence of complications when compared to open cholecystectomy. To insure such safe propagation of LC, the guidelines outlined by the Society of American Gastrointestinal Endoscopic Surgeons[14] are one standard that we think is appropriate. These include recommendations for a working familiarity and competence with diagnostic laparoscopy by the biliary surgeon before any attempt to perform LC.

There is no place for the performance of LC by any persons other than appropriately trained and experienced biliary surgeons or those undergoing a full-time training program to obtain such skills. Lack of adherence to this principle by the medical community will almost certainly result in a sharp increase in complication rates and would have no basis in terms of the accepted standard of surgical care for cholelithiasis.

An adequate training course in LC, including an adequate hands-on experience in a laboratory setting, also is essential for the safe initiation of LC into the practice of the surgeon who has no access to a teaching setting such as is available to a surgical resident. In addition initial proctoring is advisable for all surgeons beginning LC, both for safety and quality assurance. It is the responsibility of the academic surgical community, when possible, to offer adequate training courses in LC for surgeons working in other hospitals. We have trained 34 surgeons from other hospitals to date and will continue such programs as local need dictates.

At our medical center we have safely trained several residents (nine to date) without the use of a full laboratory training course before participating in an assisting role in the operating suite. A period of apprenticeship as an assistant is required until skill in performing the manipulation of laparoscopic instruments is achieved. As learning curves vary from individual to individual, the use of a fixed number of cases to define such skill is not as useful as the assumption of responsibility on the part of the experienced surgeon in determining when the performance of increasing portions of any LC procedure can be performed safely by an assistant still in the learning phase of the LC procedure.

From the first assistant position, the instructing surgeon skilled in LC can significantly aid the adequately apprenticed surgeon in his or her initial LC procedures. The first assistant inserts the catheter for cholangiography and is responsible for the critical exposure of the triangle of Callot or the gallbladder bed as necessary. The video monitor also is an excellent device to assist in teaching because the field of visualization is the same for all participants during LC. Through the use of these teaching principles, we have successfully incorporated resident training in LC into the practice of the procedure at our medical center. In the community hospital setting, where such training is not possible, there will by necessity need to be greater cooperation between surgeons experienced in LC and those still on their 'learning curves' if significant complications are to be avoided. Such cooperation also may be advantageous in terms of the increased number of skilled personnel required to perform LC and may become a permanent arrangement for such reasons even after both surgeons have become skilled at performing LC. Use of such means of teaching would certainly be more cost-effective for the general surgeon in practice.

Laparoscopic cholecystectomy holds several significant advantages over open cholecystectomy. The procedure addresses most of the major objections patients voice when considering a surgical approach for cholelithiasis. Patients are concerned for their safety, and this has been discussed. Other important concerns include postoperative pain, postoperative recovery, and time lost from work and daily activities. In addition some patients object to the unaesthetic aspects of a large abdominal scar. Before LC the surgical community had begun to address these concerns through the use of minicholecystectomy[15] and discharge from the hospital within 24 hours after elective cholecystectomy.[16] However, despite these measures, patients still had a significant amount of pain and a lengthy recovery time before full activities could be resumed. In addition such measures have not been applied broadly at all institutions because data show that the average hospital stay in the United States in 1988 for treatment of cholelithiasis or its sequelae was 6.1 days.[17]

Laparoscopic cholecystectomy offers the potential to decrease significantly postoperative length of stay after cholecystectomy, as shown by our data. In addition it also probably will allow a more rapid return to work for most patients. Actual data on return to full activities or work were not obtained uniformly in our series. Patients were seen in follow-up 1 to 3 weeks after surgery, and in no case was there an inability to return to normal daily activities within 2 weeks after successful LC. The vast majority of patients reported feeling 'normal' by 1 week after surgery. Many had resumed their job activities within 3 to 4 days after surgery, and in some instances even more rapidly. The objective data of the remarkably low pain medication requirements for patients undergoing LC confirms these reports.

Based on the decreased length of postoperative hospitalization, hospital costs to patients undergoing LC should be lower. This is of no small significance in an era of mounting concern about increasing healthcare costs.

Other than the potential for an increased incidence of bile duct injuries and complications, LC does have a few inherent disadvantages from some surgeons' points of view. Optimally the procedure requires three skilled people to perform it well. A skilled surgeon, assistant, and camera operator are all important to the success of the procedure. Maintaining the availability of such a large team may be difficult for the individual surgeon in a community hospital setting.

Economic considerations in terms of start-up costs for LC also may pose a problem for smaller hospitals or surgical groups. It is estimated that a full set of equipment to perform LC currently costs a minimum of $35,000.00 to $40,000.00. Such large initial expenses may overburden hospital budgets. Procurement of such equipment may force hospitals to increase technical charges for the use of such equipment to recover initial outlay costs, which could lessen the potential savings from the procedure. The excess demand and limited supply of such equipment has not created any significant competition among suppliers and decreases in equipment costs are unlikely until such an economic situation occurs.

No laser of any type has been used in our LC experience to date. Our data demonstrate that monopolar cautery has proved safe and effective in allowing dissection of the gallbladder from the liver bed during LC. Its use is simpler and safer in the setting of training residents to perform

LC. The additional expense of using a laser for LC, both in terms of the initial outlay costs and subsequent user fees that would be charged to each patient, are not justified. Elimination of the routine use of lasers in LC procedures could decrease costs and prevent what may be an overuse of highly expensive technology.

Increased operating time is a potential criticism of LC. Our data clearly show that the use of intraoperative cholangiography significantly lengthens operative time. This finding is not surprising because the same is true for open cholecystectomy. There have been many articles in the literature on the merits of routine *versus* selective cholangiography. Our data do not address this issue other than to confirm the increased operative time. Generally we have used or attempted intraoperative cholangiography. Our reasons for doing so include the additional margin of safety the cholangiogram may give in confirming the biliary duct anatomy. The length of the cystic duct present and available for the placement of clips is useful information obtained from the cholangiogram. In addition the benefits of teaching our residents the ability to perform intraoperative cholangiography during LC are significant and not to be ignored. Intraoperative cholangiography probably should be included routinely as part of LC early in each surgeon's experience until this aspect of the operation is well mastered and until enough familiarity with LC has occurred to allow reliable methods of identification of the necessary anatomic structures for safe cholecystectomy.

Our data were analyzed as to the effect of increasing experience with LC on operative time. It was expected that increasing experience might result in faster conduct of the procedure, but in no surgeon's individual series was the second half of his experience significantly faster. Only one surgeon's second half experience was even close to achieving statistical significance, but the probability value was 0.13. In addition there was not a significant decrease in operating time with increasing experience when the series as a whole was compared using each surgeon's experience as a data point. The data suggested a pattern of such a possibility, but again the probability value was only 0.10.

Several explanations exist as to why there was no correlation seen between increasing experience and decreasing operating time. The regression analysis had only four data points and this low number may have contributed to the lack of statistical significance. In addition another probable explanation for these findings are that in virtually all, except the first few, cases in the series, the operating team for LC procedure was periodically undergoing change. A total of nine residents were involved sufficiently in the series to have received enough training to have a basis for performing LC in the future. The constant necessity to train new team members, the incorporation of two attending surgeons into the series with their learning curves, and the above-mentioned tendency to favor intraoperative cholangiography may all have been factors influencing the length of operative time.

Other factors that were shown clearly to influence the length of operative time included the presence of acute cholecystitis and the presence of preoperative elevation in liver function tests. Clearly the acute gallbladder is more difficult to remove than the uninflamed one, using any operative approach, so this finding is not surprising. Preoperative increases in liver function tests probably indicated increased severity of disease, with increased adhesions, scarring, or manifestations of either mild acute or chronic cholecystitis. The group of patients who were noted to not have any significant adhesions to the gallbladder or chronic scarring had, as would be expected, a significantly shorter operative time than did those with adhesions or scarring.

Criteria for patient selection for LC are still under evaluation. Initial reports suggested that the procedure should be avoided in obese patients, but we found no significant increase in the incidence of conversion to open cholecystectomy in those patients weighing more than 200 pounds. Similarly coagulopathy, a contraindication in some preliminary reports on LC,[5] has proved not to be an absolute contraindication in our series, as demonstrated by the successful performance of LC for a patient with severe von Willebrand's disease. Upper abdominal scars and scars near the umbilicus were intimidating initially. However, with increased experience, it is now routine to assess the adhesions and scarring within the peritoneal cavity before abandoning the possibility of performing LC.

Acute cholecystitis poses a more difficult than usual situation for the successful completion of LC, as documented by the much higher rate of conversion to open cholecystectomy in this patient population. Successful completion of LC in this clinical setting is probably only done in a high percentage of cases by surgeons experienced and skilled at the technique of the procedure. Laparoscopic visualization of the gallbladder in patients with clinical signs of acute cholecystitis is probably always warranted, however, even in the hands of surgeons with modest but not expert skill in performing LC. This is based on at least one patient early in our experience who was arbitrarily denied an attempt at LC based on such a picture, only to find at open cholecystectomy that the degree of inflammation was so mild that LC probably would have succeeded. During a surgeon's early experience with LC, the laparoscopic observation of a very edematous, necrotic, or severely inflamed gallbladder with significant surrounding adhesions probably should be a signal to convert to an open procedure at the first sign of operative difficulty in attempting LC.

The list of absolute contraindications to attempting LC clearly diminished with increasing experience with the procedure, making LC applicable to nearly all patients with symptomatic cholelithiasis. At present we exclude those patients who require concomitant upper abdominal operations and those unable to tolerate general anesthesia. The latter condition could presumably also be overcome in selected cases with the use of an adequate level of epidural anesthesia.

These data reflect the fact that most patients require a minimal hospital stay after LC. Only those patients with severe concurrent medical problems seemed to require additional recovery time. Although it cannot be proved by these data, it is possible that these patients would have required an even longer postoperative hospital convalescence if they had been treated with open cholecystectomy. Therefore, for the uncomplicated patient, the data justify concluding that a very short postoperative stay is expected, and patients can be so counseled. Two of our patients have been discharged the day of surgery and the percentage of such same-day discharges is higher in other reported series.[18] Evolution to the use of LC as an ambulatory surgical procedure for the selected low-risk patient is not unlikely based on this initial experience.

Laparoscopic cholecystectomy offers all the efficacy and safety of traditional cholecystectomy without many of the undesirable aspects of surgery in terms of pain and convalescence. As such clearly it should limit the recent trend in the last decade of the use of nondefinitive nonsurgical means of treating gallstones. Experimental procedures, such as the use of methyl *tert*-butyl ether,[19] which require a hospitalization period of several days, risk of morbidity, which is not less than that reported for LC, and a nondefinitive result with the significant possibility of gallstone recurrence certainly appear no longer justified. The success of LC also must raise the question of the cost-effectiveness of the increasing trend of using oral bile salts as an initial treatment for symptomatic cholelithiasis.

Due to its ability to lessen markedly the undesirable aspects of surgery, LC has become, in our geographic area, the clear choice of informed patients. Most patients seen in the clinic for evaluation for elective treatment of cholelithiasis have come due to previous knowledge of the availability of LC. As the medical community and the public become more informed about LC, the demand for it probably will increase.

Laparoscopic cholecystectomy marks, in many instances, the introduction by the general surgeon in practice of the routine use of an endoscopic technique. Once familiarity with LC is mastered, it is predictable that the general surgeon will use laparoscopic techniques and a 'minimal access'[7] approach to the advantage of his patients in other areas where they clearly can be applied. The evolution of minimal access surgery is probable in the years ahead.

Based on the data presented, we conclude that laparoscopic cholecystectomy is a safe surgical means of removing the gallbladder with resulting significantly decreased length of postoperative hospitalization, requirements for pain medication, and postoperative length of convalescence when compared to open cholecystectomy. As such laparoscopic cholecystectomy is the treatment of choice for symptomatic cholelithiasis.

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DISCUSSIONS

DR. JAMES THOMPSON (Galveston, Texas): We need all to recognize that we are facing a watershed. I do not know how many chairmen, when first hearing about laparoscopic cholecystectomy, came to the immediate and absolutely wrong conclusion as vocally as I did.

This is an opportunity to say mea culpa. Fortunately we have in our department a fairly advanced state of what I would call loyal anarchy. And Sally Abston and Bill Nealon, among others, convinced me that I was absolutely wrong. And I think we need to think about this for nearly everything we do.

I was certain that this would not work. I do not know that we are going to be able to fix an aortic valve through a thoracoscope, but I would bet that we will be able to do many things that we never thought would be possible, and I suspect that our patients will greatly benefit from application of these techniques.

I would like to join others in saying that we ought to forget about the laser. That is some kind of gimmick; the cautery works just splendidly.

I had some sort of tribal suspicion that there was extortion going on with these disposable apparati, and I am glad to hear that vocalized here because I think that is another great waste of money.

It will be very important for us to see that surgeons who do this procedure are trained. Never in my experience has anything so burst on the firmament as this operation. If this had originated in an academic institution, this series of papers would not have been given for 3 years. I will just tell you that because we would have been worried about how things had—but the fellows who got into the work were enthusiasts. Their motives were to get things done quickly, and they did, and they dragged academicians into it kicking and screaming.

I would like to know, Dr. Meyers, who, in April 1990, had accumulated 400 of these, because I would have to tip my hat to him.

Finally in the development of any new idea there is apt to be an inevitable swing. I mentioned this in passing last year when we were talking about bacterial translocation. And I will tell you, in that situation, we were at least approaching panic.

And that is exactly where we are, I think, with lithotripsy. I suspect, as others have said, that now laparoscopic cholecystectomy is here to stay. But I think that anytime any new idea reaches such a pinnacle of enthusiasm, we must realize that it will eventually find its place with a few swings of the pendulum.

Regarding the matter of common bile duct stones, to say that a patient does not have a stone, that almost requires an autopsy. It is really very difficult to say a patient does not have a stone. You could make a very good case for requiring, in the training, that everyone learn routinely to do laparoscopic cholangiogram.

DR. J. KENNETH JACOBS (Nashville, Tennessee): At St. Thomas Hospital in Nashville, we have performed 381 laparoscopic cholecystectomies since we began our program in January 1990. These have been carried out while training 10 attending surgeons and 12 residents to perform the procedures.

Most of the points that I wished to make about the procedure have been covered by other discussants. I would only like to add our thoughts about cholangiography.

Cholangiography has been attempted in 301 of these patients and was successful in 262 of them, or 87%. We think cholangiography should be performed wherever possible, not only to determine the presence or absence of common duct stones but also to confirm the ductile anatomy as viewed on the monitor.

Experience gathered from doing easy cholangiograms becomes invaluable in patients with acute cholecystitis, where the ductile anatomy is often obscured.

DR. BRUCE SCHIRMER (Closing discussion): Dr. Voyles we do not routinely use the disposable trochars. We routinely use the nondisposable trochars for most of our cases. I can perhaps think of some instances in which the disposable trochars may be of some benefit. Patients with infectious conditions may be one indication for using them.

Another advantage the disposable trochars have is that it is simpler for the nursing personnel to clean and to change over instruments between cases if they do not have to worry about cleaning the nondisposable trochars. However, despite these factors, we have generally used the nondisposable trochars.

Dr. Adams asked whether cholangiography prevents common bile duct injury. In our series we had one common bile duct injury, and that was one of my own cases, so I can comment on that personally. I do not believe that the cholangiogram in that case was a significant factor. The injury was caused by dissection using a pair of scissors behind the cystic duct before the cystic duct was divided. And once the cystic duct was divided, we could see a small laceration in the side of the common bile duct.

Another aspect to that injury was the fact that it was the first case we asked a visiting professor from outside to watch. Embarrassing moments seem to occur with high frequency in such situations. Another factor, though, that does bear on the issue of cholangiography is that we have had at least one case in our series in which the cystic duct came off the right hepatic duct. That was diagnosed by intraoperative cholangiography and perhaps prevented an injury to the biliary tree in that situation. We continue to advocate the use of intraoperative cholangiogram in our practice. That is for several reasons. One is that we are constantly involved in teaching not only new faculty members but new residents as well. We now have trained nine residents and several faculty members after the first two of us started the procedures. With that increased number of people, we felt, as other commentators have already noted, that the need to learn intraoperative cholangiography under controlled conditions is important because the time you need it is not the time to start learning how to do it.

Dr. Adams also asked if increasing experience and equipment improve the incidence of intraoperative cholangiography. The Olsen cholangiocatheter clamp has helped us with our success rate of doing intraoperative cholangiography, so from that aspect, yes, improved equipment does improve the success rate. Increasing experience probably was an important factor, but, again, our data do not corroborate that because we are constantly in a teaching mode.

I would agree with Dr. Wilson's comments that surgery will be remarkably changed by the addition of video surgery to our armamentarium of techniques, and that will certainly bear an important influence on the future.

There is evidence that, as Dr. Cushieri first coined it, "minimal access" surgery will be the trend of surgery in the next 20 years. There will be more and more procedures that are amenable to minimal access approaches or laparoscopic approaches.

I disagree with Dr. Chavez's comments about the similarity of recovery from mini-cholecystectomy compared to laparoscopic cholecystectomy. In our experience there is a significant difference in the ability of patients to return to work, and there is a significant difference in their postoperative narcotic requirements and their level of pain. There may not be with changing attitudes, as much of a difference in discharge from the hospital, but certainly we do think there is a difference in the absolute recovery of the patients.

I'd like to close by thanking Dr. Thompson for his comments and concurring with the fact that we do need to analyze and determine to which areas laparoscopic surgery can be applied in the future. There are certainly many procedures that we are doing that are amenable to its application, and as the technique becomes more familiar to many gifted and talented general surgeons across the country, we will see the evolution of including this technique in more and more operations.

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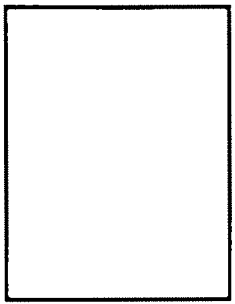

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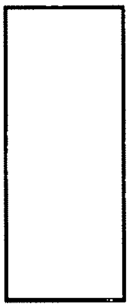

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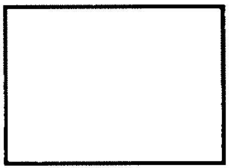

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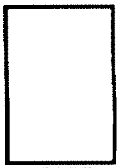

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